SACHRP Minutes, February 28-29, 2012

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Secretary's Advisory Committee on Human Research Protections (SACHRP)
Tuesday, February 28, 2012 – Wednesday, February 29, 2012
Minutes

Voting SACHRP Members Present:
Barbara Bierer (Chair), Albert J. Allen, Carl H. Coleman, Gary L. Chadwick, David G. Forster, Gary H. Gibbons, Steven Joffe, Susan Krivacic, Suzanne M. Rivera, Lainie F. Ross, Stephen O. Sodeke

Tuesday, February 28, 2012

Welcome: Opening Remarks
Barbara Bierer, M.D., SACHRP Chair

Dr. Bierer welcomed attendees to the 28th meeting of SACHRP and reviewed the agenda.She said she would welcome suggestions for future panels or topics SACHRP should address.

The minutes for October, 2011 were approved with the following changes.

- p. 25: Ms. Decot, ex officio representative for the Department of Defense, said the agency would have trouble with some criteria *in the ANPRM*, but the new *Department of Defense* policy would be expected to offer some latitude when collaborating.

- p. 20, top of page: approved *unanimously.*

- p. 9. Dr. Chadwick...*did not support* the idea that audits can be used....

The Chair thanked Julia Gorey and Cecilia Chirinos, OHRP staff assigned to SACHRP, for their critical help in preparations for the meeting.

Report of Issues
Jerry Menikoff, M.D., J.D., Director, Office for Human Research Protections (OHRP)

Dr. Menikoff welcomed everyone and thanked subcommittee members for their intense work behind the scenes. He reported that OHRP has been engaged in educating people about policy issues. Divisions within OHRP collaborated on OHRP's first webinar. They estimate over 1,000 people participated. This approach makes it easier for many people to learn about regulations and ethical issues at a relatively low cost.

Presidential Commission for the Study of Bioethical Issues: Moral Science: Protecting Participants in Human Subjects Research

COL Nelson Michael, M.D., Ph.D., Director, Division of Retrovirology, Walter Reed Army Institute of Research

Note: PowerPoints for all presentations are posted on the OHRP Web site. Please see these resources for more detailed information.

Following the revelation of "highly questionable" research funded by the U.S. Government conducted in Guatemala in the late 1940s, the President asked for several studies focused on ethical issues in research. The Presidential Commission for the Study of Bioethical Issues was established to complete these studies. Reports issued to date address the following area:

1. A review of contemporary studies funded by the U.S., whether conducted domestically or internationally. This was known as the Human Subjects Research Landscape Project. This report, "Moral Science: Protecting Participants in Human Subjects Research," was issued in December, 2011.
2. A historical investigation to understand the thinking behind what happened. This report, "Ethically Impossible" STD Research in Guatemala from 1946 to 1948," was issued in September, 2011.
3. A review focusing specifically on ethical issues in research funded by the U.S. and conducted in other countries. This report, "Research across Borders: Proceedings of the International Research Panel of the Presidential Commission for the Study of Bioethical Issues," was issued in August, 2011.
4. A review of ethical issues in new biological research, "New Directions: The Ethics of Synthetic Biology and Emerging Technologies," was issued in December, 2010.

All reports and additional information on the Commission may be found at:
http://bioethics.gov/cms/studies

Recommendations from the International Research Panel include the following:

1. Researchers must demonstrate respect for human subjects and their communities in all phases of clinical trial design and implementation. Recognizing other cultural standards and practices through community engagement is one concrete means of showing respect.
   - Ongoing international dialogue between U.S. and international bodies is critical to protecting human subjects in research.
   - U.S. and foreign investigators would benefit from clarification of the U.S. regulatory exception for foreign *"protections that are at least equivalent to those"* in the United States ("equivalent protections") found at 45 C.F.R. § 46.101(h) and how it can be applied.

2. Funders of human subjects research should support ethics training for investigators and others, including IRB members.

3. Greater efforts are needed to enhance transparency, monitor ongoing research, and hold researchers and institutions responsible and accountable for violations of applicable rules, standards, and practices. To enhance transparency and accountability, governments should consider requiring all greater than minimal risk research to be registered and results reported.

4. The United States should implement a system to compensate research subjects for research-related injuries.

5. Continued efforts to harmonize and guide interpretation of rules should be made a priority over creating new rules.

COL Michael noted that the fourth recommendation was controversial and unity was hard-won; while compensation seemed intuitively clear and appropriate to overseas partners, the idea was new to the U.S.

The Human Subjects Research Landscape Project found a lack of systematic data available across all Federal agencies and departments related to their scientific studies with human subjects and noted that the internal systems of the agencies involved were highly variable. Many agencies could not readily provide all requested information. Commission appointees found that the current U.S. system "provides substantial protections for the health, rights, and welfare of research subjects; and serves, generally, to protect people from harm or unethical treatment." However, the currently limited ability of some governmental agencies to identify basic information research qualifies this conclusion.

Recommendations from this panel covered 14 areas:

- Recommendation 1: Improve Accountability through Public Access
- Recommendation 2: Improve Accountability through Expanded Research
- Recommendation 3: Treating and Compensating for Research-Related Injury
- Recommendation 4: Treating and Compensating for Research-Related Injury Follow Up
- Recommendation 5: Make the Ethical Underpinnings of Regulations More Explicit
- Recommendation 6: Amend the Common Rule to Address Investigator Responsibilities
- Recommendation 7: Expand Ethics Discourse and Education
- Recommendation 8: Respect Equivalent Protections
- Recommendation 9: Promote Community Engagement
- Recommendation 10: Ensure Capacity to Protect Human Subjects
- Recommendation 11: Evaluate Responsiveness as a Condition for Ethical Site Selection
- Recommendation 12: Ensure Ethical Study Design for Control Trials
- Recommendation 13: Promoting Current Reform Efforts
- Recommendation 14: Responding to Recommendations.

DISCUSSION

Dr. Bierer praised the Commission for a "body of terrific work" that "sets the path forward for all of us." She inquired about the extent of the Commission's authority, asking specifically whether the White House's Office of Science and Technology Policy (OSTP) is required to respond officially to its recommendations. COL Michael responded that the Commission is an advisory committee with a mandate from the President, putting it in a strong position. He said OSTP has been an effective partner and noted that representatives of the Federal government participate in the studies. The fact that the National Institutes of Health have allocated $1 million to study regulatory changes related to Continuing Review is an indication of strong commitment to exploring needs.

Dr. Chadwick observed that many of the recommendations have been suggested by other groups. He expressed strong personal support for recommendations 13 and 14. He also noted that of the seven areas addressed by the recent Advance Notice of Proposed Rule Making (ANPRM) from OHRP, five were supported by the Human Subjects Research Landscape Project. He asked whether members considered the universal application of human subject protection regulations and regulations regarding the Health Insurance Portability and Accountability Act (HIPAA). COL Michael said the omission of recommendations in these areas did not suggest lack of support, but simply a need to focus on particular issues, especially those raised by the Guatemala study that resulted in the Presidential charge.

Funding for treatment of research-related injuries. Dr. Rivera applauded Recommendation 3 and asked whether the intent was that treatment would be paid for only if subjects were participating in Federally funded research. In addition, she wondered whether treatment would be directly chargeable to grants. Noting that Federal agencies do not currently budget for treatment even of injuries to subjects that occur as a result of study participation, she wondered how expenses should be born. COL Michael referred Dr. Rivera to the Commission's Boston meeting in November of 2011: http://bioethics.gov/cms/meeting-seven. A series of speakers representing the pharmaceutical industries spoke to the issue. Some representatives of academia were concerned that the high cost would restrict the amount of science that could be done. However, the University of Washington gave a presentation that described the system they have used for ten years, in which a large healthcare system is able to address research-related injuries without the need to prove negligence. They took this approach after a business case analysis showed that this was actually less costly than engaging an insurance company. He said this model might provide a template for how the recommendation would be placed in practice. Dr. Chadwick added that the University of Rochester has followed a similar policy for 15 years. Mr. Forster suggested that SACHRP address the issue of how subjects' treatment costs could be handled.

Public accountability. Dr. Bierer asked why the Commission suggested a portal for access to human subjects research data be available through OHRP rather than clinicaltrials.gov. The speaker said that people are used to going to the OHRP site.

Establishing agency policies. Dr. Joffe asked about the role of OSTP in establishing policies across agencies. COL Michael said his personal opinion was that HHS would be more likely to do the "heavy lifting" involved in followup.

Role of industry and FDA. Dr. Bierer observed that almost all industry-related research is regulated by the FDA. However, it may be problematic that different standards apply to such studies. The speaker agreed that this was problematic, adding that much research done by the pharmaceutical industry is not regulated by FDA because it is done outside the U.S. for drugs that will not be marketed in the U.S. He said industry had been responsive and helpful in the study.

Equivalent protections. Ms. Krivacic highlighted the need for cultural education as an adjunct to Recommendation 7. She noted that the current position tends to be "our money, our rules." There is a need to consider reasonable standards established elsewhere. For example, Great Britain believes that Continuing Review every 3 years is adequate.

COL Michael said his agency, the Walter Reed Army Institute of Research, does a substantial part of its research oversees and finds that cultural sensitivity is critical. Ethical approaches that are acceptable to the community may not be acceptable to the researchers, and vice versa. Dr. Allen said that industry needed to follow guidelines that parallel those of the FDA when working overseas.

Mr. Forster highlighted the wide range of existing human subject protection policies internationally. The speaker agreed, but noted that many countries have protections as good as ours. It is important not to let expediency drive site selection.

Dr. Bierer asked whether the Commission had a process in mind for determining whether or not protections were equivalent. The speaker said the Commission did not have time to flesh out a specific approach.

Community engagement. Regarding Recommendation 9, Dr. Sodeke applauded the Commission's support for community engagement. He noted that the involvement of leaders in Guatemala was not enough to prevent the study from going forward, but a robust community engagement process might have been successful. A SACHRP member observed that the definition of community is complex and should include more than consultation with a "community association." Dr. Bierer commented that SACHRP has addressed this topic in the past and might choose to take it up again.

Follow-up. Dr. Bierer asked how SACHRP could support the Commission, given the overlapping goals of the two entities. She suggested that SACHRP might, for example, study the issue of research-related injuries and compensation. COL Michael noted that the Commission's offices are near HHS and a closer liaison with SACHRP would be welcome, especially to exchange information. He added that SACHRP has a different mandate and could choose to explore any of the issues raised by the Commission in more depth. He noted there was "strength in synergy."

Dr. Bierer asked SACHRP members and ex officios to identify topics for panels and other follow-up SACHRP might wish to pursue. Suggestions included:

1. SACHRP could articulate specific recommendations regarding investigator responsibilities. Mr. Nelson reminded SACHRP that recommendations have been presented by SAS but were not approved.

2. SACHRP could revisit the issue of community engagement, which Dr. Bierer sees as an "unfinished" piece of work. Ms. Krivacic suggested that the site selection process could also be addressed. She noted that the sites often have resources that can be used to support the research and ensure it is both ethical and successful.

3. Ms. Decot suggested that it would be helpful for SACHRP to create a framework to facilitate review of similarities and differences in international equivalency standards.

4. Dr. Gibbons suggested further work on genes and genomics.

5. Dr. Chadwick proposed taking up the issue of compensation, noting the U.S. is "out of step with the rest of the world" on this issue.

6. Dr. Joffe suggested addressing oversight responsibilities and enforcement, including alternatives to IRB oversight. Dr. Bierer noted that SACHRP's letter in response to the ANPRM provides a good start.

Summary of Public Comment: Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators

Edward Bartlett, Ph.D., OHRP

Dr. Bartlett reminded SACHRP that the committee had requested a presentation on public comments received in response to OHRP's Advance Notice of Proposed Rule Making (ANPRM), which was published in the *Federal Register* on July 26, 2011. The ANPRM contained 74 questions developed with input from a range of Federal agencies and were organized in seven broad areas:

1. Refinement of the existing risk-based regulatory framework
2. Use of a single IRB review of record for domestic sites of multi-center studies
3. Improvement of consent forms and the consent process
4. Establishment of mandatory data security and information protection standards for all studies that involve identifiable or potentially identifiable data
5. Establishment of an improved, more systematic approach for the collection of information on unanticipated problems and adverse events
6. Extension of Federal regulatory protections to all human subjects research, regardless of funding source, conducted at institutions in the U.S. that receive some federal funding for human subjects research
7. Improvement in the harmonization of regulations and related agency guidance

Over 1,100 responses were received, a few of which exceeded 100 pages in length. Most submissions were thoughtful and reasoned. The speaker summarized comments as follows.

Risk-Based Protections: Definitions and Applicability

- *Clarifying the definition of research and broadening exemptions.* A strong majority supported clarifying the definition of research and/or broadening the exemptions. Commenters identified areas that can be removed from regulatory oversight, including: quality improvement, public health program evaluation, history/oral history, languages, journalism, healthcare operations, and other social sciences.

Risk-Based Protections: Exempt – Overall

- *Researchers determining exempt status.* A strong majority opposed the notion that researchers possess the objectivity and expertise to make an assessment of exempt status
- *Waiting period after submitting registration form.* A majority favored establishing a brief waiting period.
- *Required retrospective audits.* A strong majority were opposed to the auditing requirement.
- *Sufficiency of registration form for audit purposes.* A majority did not believe a one-page form would be sufficient to conduct an audit.

Risk-Based Protections: Exempt Category 2

- *Additional exempt categories.* A strong majority supported the inclusion of other types of research to qualify as Exempt. The most common were history, ethnography/observation, linguistics, Internet/virtual reality/online research, and QI/QA.
- *Additional excused methodologies.* A majority supported the inclusion of additional methodologies and provided numerous suggestions. A minority, however, did not believe research methodology was an adequate criterion to make an Exemption determination, pointing out the importance of taking into consideration the specific topic of the study, and whether vulnerable groups are being studied.
- *Excluding "emotionally charged" research from this Exempt category*. A majority opposed this idea.

Risk-Based Protections: Exempt Category 4

- *Use of "left-over" tissue without consent*. A strong majority was opposed to the ANPRM suggestion.
- *Use of standardized, general consent form for future use of biospecimens and data.* The majority was favorable, but there was unclarity around whether the form was intended to be required.
- *Conditions for waiver of consent for collection and study of existing data and biospeciments.* A very strong majority favored allowing waiver of consent. Respondents cited circumstances in which data are de-identified and existing 116(d) waiver criteria are met.
- *Application of new consent rules: prospective only, or "grandfathering" existing specimens and data sets?* The nearly unanimous view favored grandfathering.

Risk-Based Protections: Expedited Review

- *Applicability of criteria for approval under 45 CFR 46.111 to a study that qualifies for expedited review.* Opinion was nearly evenly divided. Among persons who advocated that some 111 criteria should not apply, the two most commonly listed criteria were "data monitoring" and "risks to subjects are reasonable."
- *Frequency of mandatory review of list of qualifying resource activities.* Recommended review periods ranged from annually to every 5 years, with a mean of 2.9 years.
- *Eliminating continuing review for expedited studies.* A strong majority favored removal of continuing review requirements for Expedited research.

Risk-Based Protections: Continuing Review

- *Requirement for continuing review for remaining study activities that would qualify for expedited or exempt categories.* A strong majority favored the ANPRM idea of not requiring annual continuing review for studies of the remaining stages should be considered as Expedited or Exempt.

DISCUSSION

Dr. Joffe endorsed the idea that the expedited list could be lengthened. He also suggested the possibility that the usual procedure could be "flipped," with studies presumed to be expeditable unless they are on a list of interventions that cannot be expedited.

Mr. Coleman asked what rationale was given for answers to Question 25, which asked what fields of study should not be covered by the Common Rule. The speaker said some commenters simply gave a list of topics or methodologies they thought should not be regulated, but a few gave a rationale. (For example, the American Association for Public Opinion Research argued that "common methods and practices of academic fields that do not typically seek, as their primary goal, to produce generalizable knowledge through interaction with human subjects" should be excluded from regulation by the Common Rule.) No one gave a broad discussion of principles that should guide this determination.

Dr. Menikoff explained that OHRP will evaluate over 1100 comments and assuming it leads to a NPRM, the department will eventually publish an ANPRM that gives the agency's official response. OHRP was delighted by the level of public response and engagement. He added that other information and viewpoints will be considered besides the comments.

Dr. Ross asked about the theoretical foundations of the changes envisioned in the ANPRM. Dr. Menikoff noted that the ANPRM contains some theory and that the theories differ depending on the topic. There is less evidence than one would desire to show what approaches are most likely to result in effective human subject protection. Dr. Joffe observed that a lot of common sense shines through the community's responses, and common sense can often guide decisions in ways theory cannot.

Dr. Allen observed that some comments reinforced the recommendations of the Presidential Commission. In particular, he pointed to an emphasis on the need to increase the understanding of the field of ethics. Currently, people are so focused on details they miss the "big picture" issues in subject protection.

Single IRB Review for Multi-Site Studies

Requiring central IRB review for domestic sites involved in multi-site research. This issue attracted a large number of comments, and revealed nearly evenly divided perspectives:

- Researchers and disease advocacy groups tended to favor the single IRB review requirement.
- IRB and institutional representatives tended to be opposed to the possible requirement, although many indicated single IRB review should be encouraged.

Selection of IRB of record for multi-site studies. Recommended criteria for selection of the IRB of record included:

1. Location of PI
2. Being accredited/meet objective criteria
3. Expertise in this area of research, e.g., oncology, children
4. IRB that is being monitored/audited by federal agency

Prevention of "IRB shopping." Responses to this question tended to parallel responses to the first question (:"requiring central IRB review…"). Some respondents indicated IRB-shopping was not a matter of concern.

Improving Informed Consent

- *Factors contributing to excessive length and complexity of informed consent forms.* Contributory factors include regulatory/legal requirements, Institutional requirements, HIPAA, and Fear of legal liability. Groups contributing to consent form length include sponsors, IRBs, and OHRP/FDA. Consent elements that contribute to excess length include detailing all research risks and the presentation of detailed study procedures.
- *Requiring investigator disclosure of financial interests in consent forms*. A very strong majority supported the requirement of investigator disclosure of financial relationships.
- *Whether proposed modifications would improve quality*. A strong majority was in favor of the ANPRM concept. Most of the persons who *opposed* the ANPRM idea still favored the general concept, but were opposed to regulatory approaches that were viewed as overly-rigid.
- *Requiring assessment of subject comprehension.* A strong majority supported the development of regulations or guidance designed to encourage assessment of subject comprehension. In contrast, some of those opposed argued the regulations already have an implicit requirement to assure comprehension ("legally effective informed consent" and "in language understandable to the subject").

DISCUSSION

A SACHRP member observed, in regard to Question 37 in the ANPRM, that it was not clear what "contemplated modifications" were presented for commenters to respond to. Dr. Menikoff said the idea of a template for consent forms was not the main point; rather, the ideas were focused on modifying the way consent forms are written so that key concepts are not buried and the reader really can make an informed decision.

Dr. Lux asked whether any of the comments on informed consent reflected the need to take subjects' decisionmaking capacity into account (the focus of a previous SACHRP subcommittee, the Subcommittee on the Inclusion of Individuals with Impaired Decision-Making in Research [SIIIDR]). Dr. Bartlett did not recall any comments that specifically referenced SIIIDR, but he said subject capacity was mentioned by a few commenters.

Data Protections to Minimize Information Risks

- *Applying HIPAA standards for identifiability to research.* A strong majority was opposed to the use of the HIPAA standards for purposes of defining the identifiability of research data.

- *Applying data security and information protection standards modeled on HIPAA.* A strong majority was opposed to the use of data security and information protection standards modeled on the HIPAA rules.

- *Additional data security and information protection standards.* A strong majority opposed additional data security standards. A smaller number suggested a range of alternative approaches.

Data Collection to Enhance System Oversight

- *Central database on adverse events and unanticipated problems.* A strong majority indicated agreement in principle, but many expressed practical concerns.

Extension of Federal Regulations

- *Extension of Common Rule to research that is not Federally funded.* Views were nearly evenly divided.

DISCUSSION

Dr. Joffe noted that the portfolio of research that is not Federally funded looks quite different from research that is Federally funded, and would include many kinds of research that are not biomedical. He stressed the importance of having a narrow definition of research if this approach is taken.

Dr. Menikoff verified that extending human subject protection to research that is not Federally funded would likely require new legislation.

Harmonization of Regulations and Agency Guidance

- *Single set of guidance.* A very strong majority favored efforts to promote harmonized guidance. Even though the question was specific to agency *guidance*, commenters often remarked on *regulatory* differences among the Common Rule, FDA, and HIPAA.

Dr. Bierer thanked Dr. Bartlett for the helpful presentation.

Subpart A Subcommittee (SAS)

David K. Nelson, M.S., CIP, SAS Co-Chair; David Borasky, M.P.H., CIP, SAS Co-Chair

Co-Chairs reviewed the charge of the subcommittee, its membership, meetings to date, and Secretarial letters that incorporate SAS recommendations.

Analysis of the Federalwide Assurance (FWA) Mechanism

At the request of OHRP, SAS considered alternatives to the current mechanism for providing "assurance," as required by legislation:

> *45 CFR 46.103(a). Each institution engaged in research which is covered by this policy and which is conducted or supported by a federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy.*

Specifically, OHRP asked whether the assurance process could be more effectively implemented and managed by being incorporated directly into the grant-making process. SAS debated the issue thoroughly, seeking input from ex officio members of SACHRP.

Questions and concerns expressed included the following:

- Shifting to the grant process would create greater administrative burden for grantees and funding agencies if instead of one central assurance contract it were managed on a grant by grant basis.
- If it were folded in rather than set aside, the perceived importance of the assurance might be diminished.
- The responsibility for compliance would need to be clarified. Under the new approach, would it lie with the institution, IRB, or investigator?
- Does (or could) the enhanced IRB registration process serve some of the needs covered by the FWA?
- The real problems may be more related to the "rules of engagement," which define the need for assurance, rather than FWA as such. At times, lack of consistent understanding across institutions.
- Would loss of the single FWA force Common Rule agencies/departments to establish their own separate assurance mechanisms?
- Would the new approach work against the goals of harmonization (SACHRP, PCSBI, ANPRM)?

Mr. Nelson noted that regulations speak of assurance, not *an* assurance. If agencies were going to create their own individual approaches to an assurance process, SAS would prefer to stick with the existing process. SAS's conclusions were that while the current FWA process is not perfect, there was no support for moving the assurance mechanism to the grant-making process. The SAS consensus was that the status quo should be maintained, but with attention to "engagement."

DISCUSSION

A SACHRP member commented that there was no clear rationale for treating this assurance or certification in such a unique way. Ms. Decot observed that researchers have a simple check box on a grant application that says they will comply with the Animal Protection Act. Dr. Chadwick wondered why such an affirmation of the institution's commitment to comply with the regulations would not suffice. Dr. Menikoff said that OHRP's proposal was driven by a desire to remove the administrative burden associated with the current system of assurances.

Dr. Joffe pointed out that the current system allows OHRP to create a comprehensive list. Dr. Bierer agreed that the capacity for oversight was a significant consideration. Another SACHRP member pointed out that not having to update the roster or deal with other institutions naming yours as their "IRB of record" would be advantages to eliminating this system. Dr. Bierer saw the issue of being listed as nonsubstantive, since an institution would not encounter liability until it actually reviewed a protocol. Mr. Nelson pointed out that OHRP has already lifted the requirement that individual reliance agreements be cited in the assurance.

Mr. Nelson observed that the regulations speak of assurance, rather than "an assurance" in the form of a document. While many SAS members initially were in favor of eliminating the assurance in

document form, they were concerned that each agency might elect to create its own written assurance. This would add rather than subtract form the administrative burden.

Mr. Forster noted that the FDA uses a different system based on the Principal Investigator rather than the institution and never seems to have difficulty locating the researcher.

While Co-Chairs said they had solicited the opinion of ex officios on this issue, Ms. Decot, ex officio representative for DOD, suggested that it would be worthwhile to ask the question SAS meant to pose a different way. She felt the point of the inquiry was not well understood and recommended a conference call focused on this topic. She said that DoD's response was only in regard to extramural research and suggested that agencies give separate responses for internal and external research. One SACHRP member suggested asking for an official agency response from each Common Rule Agency, but another was concerned that agencies would need considerable time to produce a formal response.

Dr. Bierer suggested asking ex officios to provide an agency response to a set of questions that could be shared and evaluated. The issue was referred back to SAS for further consideration.

Potential Revisions to the Expedited Review Categories

Co-Chairs reviewed the regulatory reference related to the categories:

> *45 CFR 46.110(a) "The Secretary, HHS, has established, and published as a Notice in the Federal Register, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the Federal Register."*

In 1998, the list was expanded. In a 2007 recommendation, SACHRP suggested specific changes to Category 7. At the request of OHRP, SAS suggested additional revisions to the list.

Revisions under consideration by SAS include the following:

- Allow some forms of radiation exposure (e.g., dexa scans, single x-ray) – prohibition of X rays (this would require consulting experts to help set thresholds);
- Clarify if taking *extra* bone marrow or CSF during a clinically-indicated procedure is considered noninvasive (there will differences in opinion on this within SAS, which noted that there is inconsistency across institutions);
- Add skin punch biopsies that do not require sutures (at least one IRB sees this as expeditable, but there are nuances to this procedure may make it difficult to set parameters);
- Address blood sample restrictions (for example, consider the implications of a minor change in a subject's weight);
- Clarify that research with NSR device can be approved through expedited review;
- Confirm that Humanitarian Use Device (HUD) protocols can be renewed via expedited review (SAS understands that this change would be acceptable to FDA);
- Expand/clarify Category 5 to allow data collected for research purposes;
- Include allergy skin testing;
- Include anesthesia / analgesia when procedures are otherwise on the list;

- Address long-term follow-up (e.g., oncology patients, device recipients) where data have both research value and clinical relevance;
- Include oral history (there is a lingering question as to whether this should be considered human subjects research);
- Address protocols using subject pools (e.g. Psych 101) for recruitment (some of these are being expedited now, but not consistently);
- Include more examples of social and behavioral research (e.g., ethnographic research, social networking, virtual reality, online research, on-line gaming research, deception, behavioral tasks and minimal risk experimentation(;
- Clarify that "Minor changes to previously approved research" (i.e., amendments) are changes that do not alter the risk-benefit analysis.

DISCUSSION

One SACHRP member saw no reason to exclude Psych 101 research projects simply because they recruit from pools. The member felt the risks should be assessed as for any other study. The co-chairs clarified that the suggestion was to exclude protocols creating (not drawing from) subject pools for recruitment.

Dr. Bierer suggested giving further consideration to various types of biopsies, governing principles, and guidelines for applicability. In many cases, researchers may want to draw additional samples beyond those required for treatment. Dr. Joffe agreed, stating the need for a clear principle that would help IRBs determine when an additional core for a gut biopsy changes the calculation of minimal risk.

In regard to anesthesia and analgesia, Dr. Joffe saw the need for a definite line between the two. He said anesthesia alters the level of consciousness and should not be considered minimal risk. Co-Chairs explained that the intent was to consider adding additional minutes under anesthesia on the expeditable list, not the use of anesthesia itself. Dr. Lux commented that general and local anesthesia should be considered separately. Dr. Bierer said extending the time needed to conduct an MRI would be a similar example.

Another SACRHP member pointed to the importance of considering the frequency of blood samples in determining the risk posed.

Dr. Joffe asked Co-Chairs whether the idea of considering anything minimal risk as expeditable was on the table. Mr. Nelson said it had been considered, but that SAS believes the lack of clear benchmarks can cause problems.

Dr. Chadwick noted that the Subcommittee on Harmonization (SOH) has been considering the need to harmonize definitions of "minor change."

No specific action was taken by SACHRP.

Review of Criteria for Waiver of Informed Consent

Regulatory background presented by Co-Chairs is as follows:

45 CFR 46. 116(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

- *Research involves no more than minimal risk to the subjects;*
- *Waiver or alteration will not adversely affect the rights and welfare of the subjects;*
- *Research could not practicably be carried out without the waiver or alteration; and*
- *Whenever appropriate, the subjects will be provided with additional pertinent information after participation.*

SACHRP asked SAS to examine criteria for waiver of consent given the permissibility/likelihood of substantive regulatory change. SAS reviewed points to consider in completing this review. SACHRP members confirmed that the subject was well worth pursuing. One member suggested looking at how waivers and consents work when institutions use a combined HIPAA authorization/consent form.

DISCUSSION

Mr. Forster commented that this area was really worth pursuing. Dr. Rivera asked whether SAS planned to consider how waivers and the consent process work when institutions use a combined HIPAA authorization/consent form, and Mr. Nelson responded that SAS did plan to address this issue.

Subcommittee on Harmonization (SOH): Letter on Misconduct

David Forster, J.D., SOH Co-Chair; Mark Barnes, J.D., SOH Co-Chair

Mr. Forster reviewed SOH's members, meetings, and completed activities.

Misconduct and Noncompliance in Human Subjects Research

Mr. Barnes reviewed a draft letter regarding researcher misconducts that was intended to resolve some areas that the committee felt required harmonization. The letter's focus was the intersection of the jurisdictions, regulatory processes, and sanctions of OHRP, the Office of Research Integrity (ORI), and the Food and Drug Administration (FDA), especially considering FDA's 2010 proposal on the sponsor's obligations to report data falsification.

Attachment A shows the letter as originally presented. Attachment B shows the letter as finalized following discussion. Changes made as a result of discussion appear in bold.

Ambiguities of OHRP and ORI Jurisdiction

SOH presented a variety of scenarios illustrating issues related to agency jurisdiction, each of which was discussed by SACHRP.

An investigator systematically varies a protocol from what was presented to and approved by IRB, and publishes the results; later analysis reveals that results were rendered unreliable by the noncompliance, and publication is withdrawn. Noncompliance could be related to a failure to measure at defined points, or coercion of subjects so intense as to skew survey results. Under current practice, ORI would presumably defer to OHRP in this case, although in fact the investigator has, through noncompliance with human subject protection regulations,

adulterated the study data so as to render those data worthless, and not suitable for publication.

DISCUSSION

Mr. Barnes saw the case as one in which both ORI and OHRP had some claim to jurisdiction. Dr. Bierer noted that while coercion of subjects would fall under OHRP's jurisdiction, "falsification" of data, to use ORI's term, would fall under ORI's jurisdiction. She suggested it was important to use ORI's term rather than "adulterated." She also wanted to stress that the violation was intentional and repetitive. Mr. Barnes said, however, that the language was chosen because he envisioned the case as primarily a Common Rule violation. He held that subjects have been denied promised results by their involvement in a worthless study.

Another SACHRP member said a case like this would be confusing to the institution. Typically, the IRB would probably review the situation and refer it to the research integrity officer saying that falsification of data is involved. Both institutions might pursue the violation.

Dr. Ross suggested that "simpler is cleaner" and suggested sticking to the issue of falsification, leaving aside coercion. A Co-Chair responded that the example is intended to point to a "crack" in the delineation of jurisdictions. SACHRP agreed to remove the first part of the last sentence regarding ORI, although members agreed this statement was made by an ORI representative at a previous SACHRP presentation.

An investigator falsifies informed consent forms in a study in which informed consent has been described in detail in the research protocol approved by the IRB, but study subjects were otherwise treated appropriately. In publication, the human subjects section inaccurately describes the elaborate informed consent process that was described in the protocol and approved by the IRB, but that was in fact not followed by the investigator. The IRB discovers this serious human subject research regulatory deviation, and requires, as a sanction, that the investigator not use the collected data. The study, paid for with significant federal grant funds, is now worthless. At the present time, it appears that ORI might cede jurisdiction of the case to OHRP, even though there has been falsification of documents, with significant harm to research integrity and a waste of federal funds.

DISCUSSION

Dr. Bierer wondered what the second case offered that the first case did not. Mr. Forster responded that the intent is to point to a faulty consent process in the second example, while the first case centered on data.

A SACHRP member suggested that nine examples might be overkill. Mr. Barnes explained that the first five examples were intended to show overlapping jurisdiction between agencies, while the latter examples focused on operations within institutions.

To achieve statistically significant results, an investigator fabricates research data on 50 subjects, and reports enrollment as 100. Only 50 subjects actually enrolled and completed a complicated, lengthy protocol, and the protocol had no direct benefit to the subjects. The investigator combines the fabricated data on 50 fictitious subjects with actual data on the 50 true subjects, and publishes the results. This represents both fabrication of data and the unjustifiable depriving of actual subjects of their time and trouble, with the investigator having offered false promise of scientific benefit for society or any specific population. This research misconduct would also seem to represent a serious violation of human subject research standards. If, under what seems to be customary practice, ORI and OHRP agree that only one of them will accept jurisdiction of the case, it is not clear to SACHRP how such an exclusive allocation would assert the purposes of both the Common Rule and ORI research integrity standards.

DISCUSSION

Dr. Menikoff asked how Co-Chairs would envision the issue of jurisdiction if the investigator did not fabricate data, but instead enrolled only 50 subjects. Does SOH view underenrollment as an OHRP issue? He noted that many studies underrecruit and are not especially well designed, but this is seldom viewed as a human subject protection issue. Mr. Barnes said in this case, the focus is not on underrecruitment because of inability to enroll enough subjects, but the falsification of data.

Dr. Menikoff said it was not clear that the wrong to the subjects is worse if data are falsified as opposed to the study is useless because of unenrollment. Mr. Barnes stressed that the example is an intentional deviation from a protocol. Dr. Menikoff said that regardless of intent, the wrong to the subject would remain.

Ms. Borror, who copresented with Mr. Dahlberg, stressed that ORI and OHRP usually experience little overlap. She also noted that in some rare cases, both agencies do pursue the case and neither cedes authority to the other.

Dr. Bierer said that part of the confusion for institutions has been ORI selecting what kind of things it will consider. Similarly, OHRP does not consider serious noncompliance to be research misconduct. There are many situations in which it is not clear what crosses the line. It is also not clear how specific an allegation must be for ORI to investigate. In the example being discussed, she noted, it is not clear who falsified the forms; and if this remains unknown, there is no case ORI can pursue. Dr. Menikoff said that OHRP would typically view this as a case involving falsification of data and would not pursue it. He was not sure what would be gained by OHRP involvement.

Dr. Bierer asked whether, when data are falsified or fabricated, ORI would envision reporting this to the IRB. Ms. Borror said this could be reported in cases that affect the safety of the subject (for example, if they were placed at risk by being enrolled in a study for which they did not meet the criteria). Dr. Bierer asked whether this would still be reported if the study has been over for three or four years. Ms. Borror said ORI does not recognize a time limit.

Dr. Joffe said he presumed an institution would need to close the protocol in a case like this, and he assumed the IRB would need to be involved. Ms. Borror said the key question would be whether the

study posed risks to subjects that could be considered an anticipated problem, or, alternatively, whether the violation constituted serious and continuing noncompliance.

Dr. Allen suggested it might be simpler to delete some cases. Dr. Bierer suggested completing the review of all examples before making this decision.

> *An investigator falsifies eligibility criteria information on enrollment forms for subjects, so that a full complement of subjects can be enrolled quickly. The study is conducted with multiple subjects whose eligibility criteria/enrollment forms were falsified. A research misconduct inquiry process, undertaken under ORI requirements, reveals this. Thereafter, disclosure is made to the IRB, leading to an IRB finding that multiple subjects who were actually ineligible for the study were subjected to serious and harmful research interventions. It appears to SACHRP that this incident of research misconduct also should be viewed as a violation of human subject research standards under 45 CFR 46, and would properly be handled under the jurisdiction of both OHRP and ORI as separate processes or a single coordinated process.*

DISCUSSION

SACHRP members had no initial comments.

> *An investigator fails to report serious and unexpected adverse events, as well as injuries to subjects that should and could have been avoided. Unexpected adverse events and injuries in turn were not reported in FDA submissions, and were not reported in publications. The study publications and FDA submissions erroneously indicate, in fact, that few or no serious adverse events occurred during the study. This FDA violation would also seem to constitute research misconduct and a violation of human subject research standards. It is unclear, however, how for enforcement purposes, FDA, OHRP, and ORI would interact to assure that the purposes of each office's regulations would be served.*

DISCUSSION

Dr. Joffe said it is implicit in the case that FDA has primary jurisdiction, but it is not clear why OHRP would be involved. He suggested clarifying this. Mr. Barnes said the point is not to say that OHRP should take jurisdiction or not, but rather that these are instances in which clarification of the decisionmaking process is needed. Dr. Menikoff said he thought the first two examples were relatively clear. He was concerned at the implication that underrecruitment cases should be investigated. Some harm to subjects other than the lack of benefit to society would have to be identified.

Dr. Joffe suggested removing the third case. However, Dr. Menikoff suggested it might be worth addressing the situation if there is real lack of clarity. The case should clarify that the case is not likely to be pursued by OHRP because of the lack of any increased risk of harm to subjects. Another SACHRP member suggested introducing FDA into the third case. The investigator could be

disqualified for repeated failure to follow regulations. The repeated violations could be within the same study.

Dr. Bierer asked whether FDA would involve ORI in a study. The FDA ex officio was unsure, but said the U.S. Attorney's office sometimes begins an investigation, placing the FDA investigation on hold. Mr. Barnes commented that the institution should want to know about the fictitious subjects because it would want to look very carefully at any future investigation by this individual. Dr. Bierer said that at her institution, the IRB wants to hear of any kind of problem in a study. Dr. Menikoff stressed that this is entirely appropriate. However, Dr. Bierer pointed out that sharing information on possible research misconduct may be problematic in that the processes to be followed in an ORI investigation require confidentiality.

Differences in Processes, Standards, and Enforcement

SOH presented examples illustrating how institutional officials may face dilemmas in complying with different proceedings and requirements associated with investigations by OHRP, FDA, and ORI. For example, ORI emphasizes that investigators must retain and be able to present basic data, but OHRP does not have a similar requirement. Also, a research misconduct inquiry may take 2-3 years. During this time, the research may or may not be placed on hold. ORI uses a "preponderance of evidence" standard in its conclusions, while institutions seldom if ever identify specific criteria for taking certain actions in regard to alleged misconduct. While FDA focuses on the actions of the investigator, OHRP looks to the institution. An ex officio observed that FDA has the power to disqualify IRBs as well as investigators. Mr. Barnes noted that differences in addressing confidentiality are especially acute, in that ORI proceedings must remain confidential while OHRP requires transparency. Institutions have difficulty knowing how to meet reporting requirements while maintaining confidentiality. Dr. Bierer noted that, in addition, a specific complainant and specific respondent are required by ORI, but this is not a requirement for action by the OHRP.

The examples included in SOH's draft letter, Co-Chairs informed SACHRP, are composites based on real cases.

> *An IRB investigated a situation that arose during a parallel research misconduct proceeding, but IRB findings and penalties (suspension of an investigator from conducting human subjects research for a defined period) long preceded any conclusion reached in the research misconduct process. The IRB made its required report to OHRP, which then replied by accepting the report and, upon receipt of FOIA requests, providing the report to the public. Therefore, the human subject violations that formed an essential component of the research misconduct, were already determined and information about those violations publicly available, prior to the conclusion of the research misconduct process.*

Dr. Bierer suggested adding the word "potential" before "research misconduct."

Ms. Borror of OHRP commented that when IRBs report serious and continuing noncompliance to OHRP, this is rarely if ever posted on the OHRP website. If a FOIA request were received, the report would be shared, but with redactions.

In parallel proceedings, and closely related fact patterns, an IRB and a research misconduct process led to findings that noncompliance with Common Rule standards had occurred, but research misconduct allegations were not substantiated. The IRB and the research misconduct process reached different conclusions about the basic facts of what had occurred. The project was supported by a Public Health Service (PHS) grant. The institution therefore had two differing, conflicting sets of fact findings, and was confused about what to report: reporting the IRB findings to OHRP and PHS would have been consistent with OHRP and PHS requirements, but would have reflected badly on the investigator's integrity; at the same time, respecting the finding that research misconduct had not been substantiated would have preserved the investigator's reputation but would have violated required reporting to OHRP and to PHS, as grant sponsor.

Dr. Bierer noted that IRB findings would have to report IRB findings to OHRP. To ORI, the institution would report that no conclusion was reached. The problem is how to protect reputation of the investigator. Mr. Barnes held that it would not be possible to report that the allegation was not substantiated except to ORI; however, Dr. Bierer disagreed. Both agreed that guidance was needed on reporting requirements. She pointed out that different institutions are clearly addressing these decisions differently, and this inconsistency is in itself a problem. She felt that ORI and OHRP were not yet prepared to assist institutions with such dilemmas.

Dr. Allen agreed that there is uncertainty about how to comply with the different requirements as a result of lack of guidance.

An IRB investigated fabrication of informed consent documents and related violations of eligibility criteria for enrollment, and then suspended the protocol, requiring the investigator to notify subjects of the study suspension and of the reasons for the suspension. Although the matter was referred also to the research misconduct inquiry process, subjects and co-investigators were advised of the Common Rule regulatory violations – as was OHRP in an institutional letter reporting the suspension – long before any research misconduct process had been completed. The investigator protested, suggesting that his reputation was being ruined before the confidential misconduct process had even passed the inquiry stage.

Mr. Barnes noted that respondents are likely to "lawyer up" in such cases, adding to the complexity of problems facing the institution.

In an attempt to preserve the required confidentiality of the research misconduct process, a research integrity official at the institution failed to disclose to the IRB a serious allegation of research misconduct in an ongoing study with human subjects. At the time the allegation was received, there was no indication that the alleged research misconduct could be placing subjects at any increased risk of harm, but the subsequent research misconduct inquiry and investigation produced evidence that subjects had been placed at increased risk. Had the IRB known these facts (or had the IRB known enough to have initiated its own investigation), the study would likely have been suspended, but the IRB did not learn of the research misconduct allegation until many months after it had been reported to the research integrity official. Ultimately, the investigation process resulted in a finding that research misconduct in fact had

occurred; however, by that point, the study had concluded. Subjects had been exposed to risks and inconvenience in a discredited study.

Dr. Bierer proposed removing the adjective "serious" before "allegation." She also asked that the final sentence be revised to remove the words "and inconvenience."

Specific Issues Requiring Clarity

Co-Chairs identified several questions SOH believes require resolution in regard to research misconduct:

1. Does a sufficiently credible and specific allegation of misconduct in research involving human subjects qualify as an "unanticipated problem involving risks to subjects or others or any serious or continuing noncompliance" that requires prompt reporting to OHRP?

2. How should the IRB, the research integrity officer and the institutional official interact with one another about serious allegations received in which both human subjects and research misconduct issues are implicated? Given regulatory requirements of confidentiality in the research misconduct process,[1] should a research integrity officer advise the institutional official and the IRB of allegations that relate to human subjects protections, and if, so, at what point in the research misconduct process?

3. When records and data have been sequestered, as required, in a research misconduct proceeding, what access should an IRB have to those materials, when they are needed for a related IRB inquiry?

4. For OHRP reporting purposes, corrective actions, and notification to subjects, what should an IRB do if IRB determinations are made prior to or the determinations differ from final research misconduct findings on the same factual issues?

5. To what extent should IRB determinations of serious noncompliance be factored into an institution's responsibility to "protect or restore" the reputation of an investigator who has been cleared of closely related research misconduct allegations?

6. How should a research misconduct proceeding treat IRB findings of unsubstantiated noncompliance, when the research misconduct process yields differing determinations on essentially the same evidence? Should it matter to the analysis of this question that the research misconduct process employs a specified standard of proof ("preponderance of the evidence")?

7. Should research subjects be informed if and when research misconduct has been conclusively determined in a study in which the subjects participated?

[1] See 42 CFR 93.108(b): "Except as may otherwise be prescribed by applicable law, confidentiality must be maintained for any records or evidence from which research subjects might be identified. *Disclosure is limited to those who have a need to know to carry out a research misconduct proceeding"* [emphasis added].

DISCUSSION

Dr. Bierer noted that confidentiality (as referenced in footnote 2) also applies to the complainant. She also stated that she did not find the third question compelling, since copies of materials can be given to the IRB. Mr. Barnes noted that investigators frequently question their right to access, however.

Dr. Bierer asked what "unsubstantiated noncompliance' meant in the sixth question. Mr. Barnes said that this referred to a series of events in which IRB looked into allegations and did not find the allegations substantiated. When the ORI investigates the same set of facts, the question is how IRB findings should be substantiated. The Chair suggested clarifying the meaning so it is not misread.

Dr. Joffe noted that "serious and continuing noncompliance" would trigger a reporting requirement, but does not imply risks to subjects. He asked when an allegation of misconduct would be construed as serious and continuing compliance. Ms. Borror responded that the misconduct might or might not be found to constitute serious and continuing noncompliance in regard to the Common Rule. This would be a case when, for example, the conduct has an impact on the safety of subjects. Dr. Joffe asked about cases in which the investigator does not follow the approval. Ms. Borror said failure to follow the protocol is noncompliance, and if the changes are substantive it would be serious noncompliance.

Dr. Rivera suggested that fabricating 50 subjects would be considered serious noncompliance by most IRBs, whether or not anyone was harmed. Dr. Bierer asked for verification that if the case report form were falsified, that would not constitute serious noncompliance from OHRP's perspective. Ms. Borror confirmed that OHRP has traditionally not treated it as such, though she could see the case for viewing it this way. Dr. Menikoff noted that such cases should certainly be reported to the IRB. He described this as "common sense" on the part of the institution. There would be concerns about the investigator's decisionmaking and the IRB should know of this misconduct. Mr. Barnes commented that institutions need guidance on when they can and cannot share information that might be relevant to an ORI investigation with the OHRP. Further, investigators who are the respondents in such cases may object that such information is being shared.

Ms. Krivacek brought up a recent Duke cancer study in which FDA was involved; data could not be duplicated, and individuals who were depicted as responding to treatment were allegedly not doing well at all. A lawsuit is being filed. Mr. Barnes commented that the incident might be a useful case study.

Dr. Rivera said there used to be a fourth category of misconduct in which an investigator deviated from the customary practices of his or her discipline. A number of campuses retain this type of misconduct in their policies on misconduct.

Dr. Joffe said there was a need for a pathway by which a particular investigator could be sanctioned for violations of the Common Rule. Theoretically, he or she could be barred from receiving Federal funds, but this authority has never been used. Dr, Menikoff said that OHRP's authority in regard to the institution could allow the agency to achieve the desired results.

Dr. Joffe asked how a Federal funder such as the National Institutes of Health would become aware that an investigator named in a proposal has engaged in serious and repetitive noncompliance with the Common Rule. Mr. Barnes observed that it would be good practice for an institution to report such

noncompliance. This would have to be done if the investigator were in charge of a current study sponsored by NIH that had to be halted. Mr. Barnes observed that in a perfect world, one would not construct such a way of investigating bad behavior on the part of a researcher, but since the regulatory world is constructed this way, the issue is how best to achieve the goals of investigation under current regulatory requirements.

FDA Standards and Proposed Mandatory Reporting of Suspected Falsification of Data

Mr. Barnes said the regulated community was alarmed by a proposed FDA rule that requires institutions to report suspected misconduct. SOH felt this rule would exacerbate current problems and would require premature reports. The FDA ex officio comments that the rule is intended to ensure that FDA finds out about the misconduct and is able to proceed with disqualifying the investigator. Dr. Bierer pointed out that the threshold for reporting suspicions to FDA is already very low.

Dr. Bierer requested that language be added related to "preserving the reputation of the investigator." Mr. Forster observed that earlier reference to FDA should be made in this portion of the letter. Dr. Allen commented that the latter four cases were far more impactful than the examples presented earlier in the letter. Mr. Barnes said he would revise the letter for review on the second day.

Dr. Allen observed that the heart of the issue is the need to balance, in cases of suspected or potential researcher misconduct, the need to protect human subjects, adequately investigate the potential misconduct, and protect the rights and reputation of the investigators involved. Dr. Bierer agreed and suggested that the tension should be expressed earlier in the letter.

Public comments were invited, but none were offered.

Wednesday, February 29 , 2012

Dr. Bierer welcomed two new ex officio SACHRP members, CAPT Patrice Robinson from the Agency for Healthcare Research and Quality (AHRQ) and Tom Feucht, Ph.D, from the Department of Justice (DOJ). Brenda Friend from NIH reported that the $1 million mentioned the previous day to be spent in support of the Presidential Commission is targeted specifically for bioethics research.

Subcommittee on Harmonization (SOH): Letter on Misconduct (Contined)

David Forster, J.D., SOH Co-Chair; Mark Barnes, J.D., SOH Co-Chair

Misconduct and Noncompliance in Human Subjects Research

Mr. Barnes reviewed changes to the draft letter in response to comments from SACHRP on the previous day. These included:

- Added a more general statement at the beginning making the point that the legal distinctions made by the various regulatory schemes that address violations/deviations from accepted professional research standards are designed for different purposes and do not constitute a coherent framework.

- Removed the first example from the first set of scenarios, since it did not make a unique point, and refined the second example to focus on the overlapping jurisdictions of the agencies that affect institutional decisionmaking.

- Changed the title to "Overlapping Regulatory Regimes of OHRP, ORI, and FDA Jurisdictions."

- Refined examples to clarify that studies are PHS-funded.

- In the example with the 50 true and 50 false subjects, removed the allegation that they were cheated by the investigator of the opportunity for public benefit. He recharacterized the example as a significant protocol deviation. The idea was added that subjects could be put at risk if the study is used to support an FDA application for a study building on the first.

- Highlighted FDA violations more clearly in the final example.

SACHRP had no initial comments on these changes.

Moving on to the second section of the letter, "Differences in Processes, Standards, and Enforcement," Dr. Chadwick suggested highlighting the institutional issues addressed in the section. Mr. Barnes revised the title to "Differences in Institutional Compliance with Processes, Standards, and Enforcement." Mr. Barnes explained that he has also integrated the role of FDA. He also corrected an erroneous citation in the footnotes on the earlier draft.

Dr. Bierer verified that the section assumes the current FDA regulations on reporting, not proposed changes. Additional changes suggested by SACHRP members included:

- Clarifying the reference to "relatively informal processes," which could be taken to apply to FDA's on-site enforcement actions, and
- Removing the reference to the investigator as a "bad actor."

Minor changes were made in the remaining two sections.

DISCUSSION

In regard to the specific issues to be addressed (the third section of the letter), Dr. Chadwick asked for further clarification of the meaning of "alleged but unsubstantiated noncompliance." New wording was added to the effect that alleged noncompliance was not substantiated.

Dr. Joffe observed that there is no obvious process for sanctioning an investigator whose actions arise to the level of serious misconduct for the purpose of an ORI investigation. He felt there should be a process for investigating and sanctioning persistent, systematic violations. Ms. Borror said processes do exist to sanction investigators. She said regulations allow for notification of peer groups of the investigators' persistent violations, and debarment could be recommended. However, this authority has never been used. Dr. Joffe offered to draft a brief statement on this issue.

- *Should research subjects be informed if and when research misconduct has been conclusively determined in a study in which the subjects participated?*

In regard to notification of subjects when serious misconduct has definitely occurred, Dr. Menikoff requested that SACHRP decide whether it is advocating notifying subjects, as opposed to simply raising the issue. Dr. Bierer asked whether OHRP has required notification. Dr. Menikoff said the OHRP website has been used to inform the public of significant violations. OHRP pays particular attention to informed consent issues, such as the failure to inform subjects of a significant risk. Dr. Chadwick suggested notification should occur in regard to any finding that might affect the subjects' willingness to participate. Mr. Forster commented that IRBs do consider notification in such instances, but often not when findings are made after studies are closed. Dr. Rivera agreed. She was concerned that the issue, as raised, is overly broad and might result in rigid guidance that is not helpful. Dr. Allen added that there is no reference that the criteria to be used in making the decision to inform subjects.

Dr. Goldkind (ex officio for FDA) commented that the discussion of this issue would be different if the focus were on the falsification or fabrication of data, which would be of material interest to any participant. She held that not all types of misconduct would rise to the level that would require post-trial notification. Dr. Bierer said that the best decision would be one that depends on the specific circumstances, but there should be an affirmative decision by the IRB as to whether or not subjects should be informed. A SACHRP member suggested rephrasing the question as, "under what circumstances should research subjects be informed…?" The review of the case and the determination by the IRB should be the focus of the question.

Final Revisions

Later in the meeting, Dr. Joffe presented a first draft of an additional section of the letter. As presented, it read as follows:

> *4. Investigation and Sanctions Process For Investigators Accused Of Serious Violations Of Human Subjects Regulations*
>
> *As noted previously, OHRP generally enforces Common Rule standards against institutions, while (ORI and FDA typically impose sanctions against individual investigators rather than against research institutions unless they also find failings in an institution's internal processes). SACHRP understands that OHRP does have the authority to refer egregious cases of violations of human subjects regulations in HHS-funded research to the Secretary for consideration of enforcement actions against individual investigators. However, SACHRP also understands that this authority has never been exercised. Furthermore, this enforcement pathway does not formally incorporate due process protections for investigators who are accused of serious and intentional violations of human subjects regulations.*
>
> *The situation outlined here creates a serious inconsistency in how the Department addresses various ways in which individual investigators may deviate from accepted standards for conducting research. On the one hand, the Department will sanction a PHS-funded researcher who is found, after a due process investigation, to have engaged in research misconduct (i.e., fabrication, falsification or plagiarism [FFP]). On the other hand, it is much less obvious how the Department can sanction a researcher who engages in serious violations of HHS human*

subjects regulations. This leads to the possibility, for example, that a PHS sponsor such as the NIH might be unaware of an investigator's history of serious and intentional violations of human subjects regulations when considering a grant application from that individual. This apparent gap is difficult to defend and may lead to public criticism should an example of a previous egregious violation of human subjects regulations come to light.

To address the gap described above, SACHRP recommends that the Department develop a mechanism for investigation and, as indicated, imposition of sanctions when an HHS-funded investigator is accused of serious and intentional violations of human subjects regulations. One option might be for OHRP and for HHS as a research funder to develop a mechanism for undertaking such an investigation and for recommending appropriate sanctions.

Dr. Joffe explained that this section was intended to address investigators that engage in serious and intentional violations of human subject regulations.

Several changes in wording were made, including the following:

- In paragraph 1, "<u>does</u> not formally incorporate" was changed to "<u>may</u> not formally incorporate."
- The words "by OHRP" were added to: "However, SACHRP also understands that this authority has never been exercised."
- Paragraph 2 was revised to emphasize the possibility of harm to human subjects rather than public criticism as a primary concern. However, the possibility of jeopardizing public trust was also retained.
- Language was added related to the need to communicate with other agencies regarding violations: *One option might be for OHRP and/or PHS (as a research funder) to develop a mechanism for undertaking such an investigation, for recommending appropriate sanctions, and <u>for developing appropriate communication strategies.</u>*

One SACHRP member wanted to be sure that language regarding interagency communication did not suggest this should always be the case. Members agreed the language was sufficiently open and simply requested clarification.

ACTION

The revised recommendations that appear as Attachment B were approved unanimously.

Minor Protocol Deviations

Mr. Forster noted that the proposal has been two years in development. He stressed that the focus of the recommendations was not on intentional deviations from the protocol to prevent immediate harm to subject, unintentional deviations that cannot be prevented, or traditional changes that are formally documented and approved by the IRB. Rather, the recommendations address:

- Deviations that occur because an investigator, research staff or other party involved in the conduct of research intentionally decides to deviate from the approved protocol.
- Deviations from the protocol that are identified before they occur, but cannot be prevented.

- Deviations from the protocol that are discovered after they occur.

Industry has asked SACHRP to consider this type of deviation. The classic example is when a 56-year-old who is a good candidate for research is available, but the age range is 18-55. Another common example is when a subject is caught in a snowstorm, or similar event that causes delay, and cannot make a scheduled visit. In such a case, what approvals are needed? FDA requires prior review in such a case. OHRP has advised SOH that such deviations require IRB review.

Dr. Ross suggested that protocols should be written with a "fudge factor" in mind. Mr. Forster agreed and said this was addressed in the recommendation. Dr. Menikoff noted that the unintentional deviation may lead to an intentional one. This is something the investigator can control.

Dr. Bierer observed that HHS and FDA regulations were referred to throughout. Dr. Menikoff said the correct language is that OHRP administers the HHS regulations.

Dr. Bierer asked ex officios and SACHRP members whether they had had time to read and consider the letter carefully. They affirmed they had.

A SACHRP member suggested weaving in some "grey areas," such as cases in which a subject has notified the investigator of an intended vacation. Mr. Forster said theoretically this person should not be enrolled, but this may not be common practice. He said it was addressed in the recommendations.

One SACHRP member pointed to the distinction between a one-time change and instances in which changes do result in a modification in the protocol (for example, changing the number of subjects enrolled). Dr. Ross commented that a number of minor changes at many sites might affect research integrity. Dr. Allen said that industry does not want sites to do such examples, but they are real life. For example, they encourage "windows" for visits instead of fixed times in order to allow for blizzards.

Dr. Bierer said the decision on how to handle such deviations might be different depending on whether the deviation occurred before or after enrollment. Mr. Forster suggested the procedures for arriving at the decision would probably be similar, regardless of whether or not the decision is the same.

Dr. Chadwick stressed that guidance should consider both the benefits and the burdens related to the review of minor deviations. Many such changes, he said, are not really changes that matter. Dr. Allen observed, however, that some deviations do matter and can lead to adverse events. He said the primary focus must be on patients and their safety and welfare.

Dr. Lux suggested changing the subtitle "secondary recommendations" to "additional recommendations." The former makes them sound less important. Mr. Forster said that these points were also important and should be addressed in guidance. Several changes in wording were suggested and incorporated.

Mr. Barnes thanked Mr. Forster for his persistence in pursuing the issue for two years.

ACTION

The revised recommendations that appear as Attachment C were approved unanimously.

Applicability of FDA Regulations for IRBs and Informed Consent

Mr. Forster said there are many types of activities under the Common Rule that are considered research, but many IRBs find it difficult to identify which activities are also regulated by FDA. Some exemptions that would be applicable under the Common Rule are not allowable under a "clinical investigation" subject to FDA. He said clear guidance is needed to clarify the "bottom line" on what research activities are subject to regulation by each agency. For example, retrospective reviews of clinical records are frequently problematic.

One barrier to accomplishing this clarification is that FDA has several definitions of key terms, including "human subject," "clinical investigation," and "study articles." To address this problem, SOH suggests alternative routes. One approach begins with clarifying this terminology, while a second approach would focus on specific activities and clarifying under what circumstances each would fall under FDA.

Dr. Bierer said clarifying these issues would be incredibly helpful.

Questions from SACHRP resulted in the following changes or clarifications:

- Two citations to regulations were corrected.
- Clarifying the specific recommendation (in this case, the entire letter).
- Safety AND efficacy was changed to safety OR efficacy.

Dr. Joffe suggests there might be times when FDA does want jurisdiction over retrospective record reviews, and there may be a limited class of circumstances in which a waiver or consent should be considered. Dr. Goldkind noted, however, that there is a statutory requirement that all device studies require informed consent. Internal harmonization across product types is needed to address the issue. She still saw value in fleshing out circumstances in which it would be helpful to FDA to have a waiver. Dr. Bierer asked whether the waiver might be used in trials that are not device studies. Dr. Goldkind encouraged suggestions and feedback. Dr. Bierer asked whether FDA had enforcement discretion in statutory areas. Dr. Goldkind said discretion is used in certain limited circumstances.

Dr. Joffe commented, in reference to drug and device registries, apparently consent would be required to enter into the registry. He thought the recommendation was unwise because it would be potentially crippling to the validity of such registries. He would recommend that they not be considered FDA-regulated clinical investigations. He pointed to a specific study in which data were not generalizable because certain subjects were missing from the registry. Dr. Bierer also saw the potential for bias if consent were required. Dr. Allen said there could be elements that would be addressed by a waiver; however, he was uncomfortable recommending that activities such as this fall outside FDA regulation. Dr. Bierer said her institution has taken the position that analyses of claims data are not FDA regulated.

Dr. Chadwick said a thorny issue is whether or not a "test article" is involved. He suggested changes in wording that would ask for clarification from FDA but not make a specific recommendation. Specifically:

FDA should issue guidance clarifying <u>that</u> prospective registries used to collect data regarding the safety and efficacy of FDA regulated test articles are FDA regulated clinical investigations, independent of whether the study article is prescribed or used as a result of the registry.

Revision: *FDA should issue guidance clarifying <u>whether</u> prospective registries used to collect data regarding the safety and efficacy of FDA-regulated test articles are FDA-regulated clinical investigations, particularly when the study article is not prescribed or used as a result of the registry.*

Mr. Forster said this would return to an earlier version of the letter, but SOH had moved on to a version that includes recommendations. He proposed not making the change in order to preserve a consistent format. Dr. Chadwick was not sure that SACHRP was the correct body to make this determination.

The Chair took a "straw poll" on the issue of whether registries are FDA regulated when the use of the test article is a follow-on to clinical care. Five people felt such registries should not be FDA regulated. Dr. Allen noted that in the academic world, such a study could be done under OHRP. He asked about the case in which the registries are run through a third party. Mr. Forster said the most important thing is to bring up the case to FDA for clarification. Dr. Bierer said the first principle was that such registries should be reviewed and under the oversight of an IRB. They should also operate under conditions under which important results should be presented to the FDA. After discussion, Dr. Bierer suggested the use of the word "whether" would allow the letter to go forward, even though the recommendation structure would not be parallel. SACHRP members agreed.

Dr. Menikoff asked whether registries always had to have identifiable information. He noted that there might be a way to have a study under the Common Rule rather than under FDA's rules. He said such a registry, with a one-way link, would not fall under the Common Rule. If no human being ever sees a name, even if it is being accessed for clinical purposes, it is possible to get around the issue of bias and the possibility of violating rules. Dr. Joffe said that in many cases, people do have a need to maintain and access identifiers, so this would not solve the problem for registries in general. Mr. Forster said FDA could decide to define "human subject" in such a way that there is no human subject without identifiers. Dr. Joffe suggested that someone entered into a registry for safety events after receiving a drug or device may not in fact be a "human subject."

The following recommendation was added:

> FDA should clarify whether the definition of human subject should include consideration of whether or not the data are identifiable. If a link is not maintained or there is only a one-way link, then perhaps the humans would not be subjects under the FDA definition of a human subject. If a link is maintained, at what point do they become human subjects under the FDA?

Mr. Barnes observed that FDA does not have a waiver except in emergencies, and a SACHRP member suggested that it should be a recommendation that the statutory changes be made to allow this option. He suggested that a footnote be added noting that the approaches described are workarounds necessitated by the lack of a waiver option. Mr. Forster observed that this was not the case in every instance.

Dr. Rivera described a scenario in which the registry is implemented by someone not involved in the original clinical trial. In this case, too, Dr. Bierer said the investigator is likely to want to be able to submit data to the FDA, and informed consent would be required.

ACTION

The revised recommendations that appear as Attachment D were approved unanimously.

SACHRP Recommendations on Treatment Use

At October 4, 2011 SACHRP meeting, FDA asked for recommendations regarding single patient treatment use of investigational drugs and biologics. They would like to improve access to study articles for compassionate use purposes. FDA recently revised its regulations on treatment use to insert a new section allowing individual access to products in life-threatening situations. FDA may authorize "expanded access" to trials of investigational drugs or biologic products (21 C.F.R. 312.300 [2011]) to treat patients with serious or life-threatening diseases or conditions who have no satisfactory or comparable alternative therapy to diagnose, monitor, or treat the disease or condition. When this is done, FDA must ascertain that the following are true:

1. The patient has a serious or life-threatening disease or condition and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
2. The potential benefit justifies the potential risk and that the risks are not unreasonable in light of the disease or condition to be treated; and
3. The provision of the investigational product will not interfere with the clinical investigation that could support marketing approval or otherwise compromise potential development.

Currently, there is confusion as to what steps are needed to make products available in these cases. Often, requests for access do not fit usual IRB criteria for approval, they are outside the norms for sponsors, are difficult for investigators, and challenge would-be subjects to find their own IRBs and often pay for review. FDA asked the following specific questions:

- What is the Committee's experience with IRB reviews of expanded access protocols?
- How quickly are they reviewed?
- Is there a charge to the individual?
- Are expanded access protocols able to be scheduled ahead of studies already on the calendar?
- Does providing for something like expedited IRB review seem a reasonable solution, based on the problem cited?
- If a reduction in the number of IRB members to approve an expanded access protocol is satisfactory to the Committee, does the Committee believe that mimicking the expedited review procedure is the best approach?
- What is the Committee's opinion on the risk/benefit analysis of expanded access protocols following the IRB procedure discussed in this presentation?

Mr. Forster said SOH recommends that "granular" guidance be issued on the steps required in various circumstances that is understandable to patients, IRBs, sponsors, and investigators. SOH also suggested that FDA should honor substance over form. There should be some review mechanism to protect patients, but that may not be a convened IRB. This might be review by the Chair or another

IRB member with appropriate expertise. FDA might also waive the requirement for informed consent. Another option is review by a designated IRB specializing in such cases. Finally, FDA could waive IRB review altogether.

DISCUSSION

Dr. Bierer suggested that SACHRP's recommendations be expressed more clearly in the document. Dr. Rivera said SACHRP should clarify whether it considers these cases to be treatment or research and take a consistent position, possibly proposing changes in the regulations. She felt SACHRP should make a specific recommendation rather than asking for guidance.

Dr. Allen commented that generalizable knowledge does result from single-use cases and they should go through an IRB. He said such cases are on the borderline between research and treatment; doctors do share the information, which is useful. Dr. Joffe disagreed that the cases constitute research and said the Common Rule was not relevant to the need to address the acute need for patients to access unapproved drugs for treatment under specific circumstances. Therefore, the logic appropriate to treatment rather than that of research should apply. Mr. Coleman pointed to the need to differentiate the IRB's role in reviewing individual treatment uses, where the focus should be exclusively on the best interests of the individual patient, from its role in reviewing research, where risks to subjects can be balanced against potential scientific benefits.

Dr. Menikoff reflected that appropriate measures follow from determining the regime under which the product is being supplied. If the patient is told that the product is appropriate treatment for his or her circumstances, then it should not be considered research. However, the treatment approach should be reasonable. Dr. Bierer observed, however, that the drugs are used in cases in which there is no established standard of care. Informed consent is relevant because use of the product is not within the scope of practice. She suggested adding such cases to the "expedited" list. However, Dr. Menikoff asked why the "expedited" approach would be appropriate if product use is not research. Dr. Goldkind added that the expedited approach would not be appropriate because product use would entail greater than minimal risk to the patient.

Dr. Goldkind (ex officio, FDA) said FDA had struggled with the issue of how to protect desperately ill patients whose use of the product is a deviation from the standard of care. FDA did not see any generalizable knowledge coming from single use of the drug. Some reporting mechanism was needed, and the IRB seemed a reasonable mechanism. Dr. Joffe agreed that good record keeping was an important part of any approach.

SACHRP members agreed that the use of the product in these cases should not be considered research, but rather investigational use of a drug that falls under FDA's authority and that involves the IRB because it has the expertise to ensure the consent documentation is clear and appropriate.

Several changes were made in the document to address issues raised in the discussion. These included:

- Adding a framing paragraph: "SACHRP notes that as a threshold issue, single patient access use does not involve the conduct of "research" as defined at 45 CFR 46 because there is no intent to develop generalizeable knowledge. Rather, this issue arises out of the FDA prohibition on the use of unapproved drugs, which requires that any use of an investigational

drug must currently be considered within the regulatory framework for clinical investigations, primarily 21 CFR Parts 50, 56, and 312."

- Citing the Belmont Report's comments on significant departures from standard practice. Members disagreed on whether it was helpful or "taken out of context," so a vote was taken on its inclusion. The majority found it helpful to include.

- Suggested expedited review as an alternative approach, but one that would require regulatory changes.

- Suggested that informed consent requirements be tailored to this circumstance, since some were not relevant.

ACTION

The revised recommendations that appear as Attachment E were approved unanimously.

Re-Examining Component Analysis

David Forster, J.D., SOH Co-Chair; Vice President, Office of Compliance, Western International Review Board; Robert J. Levine, M.D., Professor of Medicine and Lecturer in Pharmolocology and Chair, Executive Committee, Interdisciplinary Center for Bioethics, Yale University; Robert "Skip" Nelson, M.D., Ph.D., Senior Pediatric Ethicist, Office of Pediatric Therapeutics, Food and Drug Administration

Remarks by David Forster

Mr. Forster defined component analysis as "the individual assessment of benefit (prospect of direct benefit or no prospect of direct benefit) and risk (minimal risk or above minimal risk) of each intervention or procedure in a study." Many ethicists support the application of component analysis in IRB review of research with children (and other vulnerable populations), including SACHRP (in previous recommendations) and the FDA Office of Pediatric Therapeutics. However, Mr. Forster said, component analysis is poorly defined, the literature is simultaneously sparse and complicated, and the regulatory status is not clear. It is therefore difficult to train IRB members and investigators to use this approach.

The ideal outcome, in the speaker's view, would be a joint FDA/OHRP guidance explaining that component analysis is an integral part of the application of Subpart D (a "must" rather than a "should") and providing detail regarding application and documentation in IRB minutes. If this is not possible, guidance from either FDA or OHRP, or both, might be helpful.

Remarks by Robert J. Levine: Component Analysis: Evolution of the Concept

Dr. Levine noted that in component analysis, the focus is on the particular intervention or procedure, not on the entire protocol. In response to the National Commission's recommendations (1978), the regulations refer to "…interventions or procedures that [do or do not] hold out the prospect of direct benefit for the individual subject" [45 CFR 46.405-406]. The speaker argued that research never presents the prospect of direct benefit; only single interventions do that. All research, he said, has some

components that are not intended to be therapeutic. All too often, however, reviewers of a protocol find one component intended to be therapeutic, label the entire protocol as "therapeutic research," and justify it—including the non-beneficial components-- according to standards designed for "therapeutic research." Levine refers to this error as "the fallacy of the package deal." The non-beneficial components ought to be justified according to the more stringent standards designed for their justification.

Dr. Levine pointed out that resistance to application of the concept of component analysis has generally been based on two misunderstandings:

1) It is commonly misconceived as a requirement for a cumbersome process in which each component must be subjected to separate evaluation and its status as beneficial or non-beneficial formally documented. This, he asserted, is incorrect. Instead, experienced reviewers can "eyeball" a protocol and easily determine which of the interventions or procedures "hold out the prospect of direct benefit." Their judgment on this point can be corrected, if necessary, by IRB members. This is not a cumbersome process.

2) It is commonly misconceived as a "package' with 45 CFR 46.405-407. Thus, for example, those who hold this misconception think that if one finds that a non-beneficial component of a protocol designed for adult subjects presents more than a minor increase over minimal risk, then it must be subjected to a "407-review." This, the speaker asserted, is incorrect. Component analysis for research involving individuals who are capable of informed consent simply serves as a reminder that harm/benefit analyses for beneficial components differ from those that are non-beneficial.

Dr. Levine provided several examples of clinical trials in which component analysis would have provided essential clarifications. One of them was an evaluation of a thrombolytic agent for the treatment of acute myocardial infarction (MI). In this trial, the administration of the thrombolytic agent should have been justified by a different standard (reasonable possibility of personal benefit) than the repeated coronary angiograms performed to document the patency of the coronary artery (development of information that might be of value to patients with MIs in the future). Dr. Levine said that this is the way that he National Commission (1978) understood component analysis. They intended that it be applied to all research involving human subjects and recommended special additional protections related to component analysis for children (45 CFR 46.405-407) and "those institutionalized as mentally infirm" (recommended regulations were never promulgated). It was intended to serve as a corrective to the Declaration of Helsinki's distinction between therapeutic and nontherapeutic research. Dr. Levine concluded that component analysis should be applied to all proposals to conduct research involving human subjects, children included.

DISCUSSION

A SACHRP member asked about changes in the language in the 2008 revision of the Declaration of Helsinki regarding "justification by therapeutic value. Dr. Levine responded that he could not speak with authority on the reasoning of the World Medical Association's Medical Ethics Committee after 1999, the year in which the Working Group for Revision of the Declaration of Helsinki (chaired by Dr. Levine) was dissolved. He believed that the Medical Ethics Committee that reviewed the working group's proposal continued to view the relationship between physician-investigator and patient-subject as a fiduciary relationship. A careful analysis of the Declaration of Helsinki's standards for

justification of therapeutic research through the 20th century indicates that they seem to be designed for what we in the United States call "compassionate use" rather than for clinical trials.

Remarks by Robert "Skip" Nelson

Dr. Nelson defined "classic" component analysis as follows:

- A clinical investigation may include more than one intervention or procedure.
- Each intervention or procedure must be evaluated separately to determine whether it does or does not hold out the prospect of direct benefit to the enrolled child.
- Interventions or procedures that hold out the prospect of direct benefit should be considered under 21 CFR 50.52.
- Interventions or procedures that do not hold out the prospect of direct benefit should be considered under 21 CFR 50.51 or 50.53 (but not 50.52).

The speaker stressed that component analysis is important because failure to carefully distinguish the different components of a clinical investigation may result in the risks of an intervention or procedure that does not hold out the prospect of direct benefit exceeding the allowable ceiling (a minor increase over minimal risk).

He held that the "classic" approach outlined above is consistent with the recommendations of the National Commission (1978) and the resulting regulations. In public literature, however, approaches that relate component analysis to the concept of clinical equipoise[2] and a "net risks" test[3] have been suggested. Dr. Nelson stressed that in his view, neither approach offers advantages (and both have disadvantages) compared to a "classic" component analysis using the categories in 21 CFR 50 subpart D. He suggested that the current dispute about the meaning of component analysis is primarily about whether or not a fiduciary "duty of care" should be the ethical basis for research.

Dr. Nelson discussed a case in which a concerned IRB Chair contacted FDA about a proposal to use a peripherally inserted central catheter (PICC) to facilitate infusion in a multinational, placebo-controlled, study of an investigational product, in children ≥ 7 years old. The product, or placebo, was administered by IV infusion over 4 hours each day for 14 days. FDA concluded that the procedure represented more than a minor increase over minimal risk. While PICC use was justified in children receiving the active product due to the prospect of direct benefit from the infusion, children receiving the placebo via PICC were offered no direct benefit from the infusion, but exposed to greater than a minor increase over minimal risk. Thus, PICC insertion and use in the placebo group was not in compliance with 21 CFR 50, subpart D.

FDA used the case as an opportunity for an educational intervention. It asked participating IRBs whether PICCs had been used at each site, and if so, how PICC insertion was justified in the IRB's assessment of the study. PICCs were used at 19 (of over 100) sites, and approved by 12 IRBs (of

[2] Weijer, Charles and Miller, Paul B (2004). "When are research risks reasonable in relation to anticipated benefits?" *Nature Medicine*, June: 570-573.

[3] Wendler, David and Miller, Frank G. (2007). "Assessing research risks systematically: the net risks test." *Journal of Medical Ethics*, August: 481-486.

which 10 responded to FDA questions. FDA found that only two of the ten responding IRBs used component analysis in arriving at their determination, but only one used it correctly.

FDA's Draft Preamble to its Final Rule (21 CFR 50, subpart D) states:

> *Because we do not consider the administration of a placebo to offer a prospect of direct benefit, 21 CFR part 50 subpart D therefore requires that the placebo arm must present no more than minimal risk (§ 50.51) or a minor increase over minimal risk (§ 50.53), unless the clinical investigation is referred for review under 21 CFR 50.54.*

DISCUSSION

In regard to the PICC example, Dr. Bierer asked Dr. Nelson to clarify how the analysis would be different if it were risk-based or if there were clinical equipoise. The speaker referred to a debate in the literature around whether risk analysis should be conducted pre- or post-randomization. Some thought the issue of whether individuals received the placebo or not should be ignored, but this overlooked the fact that persons who received the placebo could then be exposed to more than a minor increase over minimal risk without receiving any benefit.

Dr. Bierer agreed that there was a need for better education. She felt, however, that the sponsor should have reviewed the conclusions of the 19 sites that approved the PICC insertion and should have informed the FDA. Dr. Nelson said this and other sponsors have been educated regarding this issue. Based on past experience, he doubted that sponsors could be relied on to "call" the IRBs on these decisions.

Dr. Chadwick noted that "regulation by letter" is a problem. A more effective strategy is needed to clarify the preferred approach. Dr. Menikoff said OHRP works hard not to introduce new issues in determination letters. Dr. Allen said he was glad to hear guidance was in process and supported this strategy. Dr. Bierer felt joint OHRP-FDA guidance would be the best approach. Dr. Nelson said such discussions were underway.

Dr. Levine held that if the PICC could result in large magnitude risks, even in death, it should not be standard of care. Dr. Nelson differed, noting that the PICC could be used to deliver beneficial treatment that justified the level of risk.

Dr. Bierer queried whether an IRB that did component analysis and concluded that insertion of the PICC line was no more than minor increase over minimal risk would be held to be out of compliance. Dr. Nelson said they would have done their job. He added that evaluating what constitutes a minor increase over minimal risk is not straightforward.

Dr. Chadwick noted that FDA has previously taken the position that placebo arms do confer benefits. Therefore, he asked Dr. Nelson to consider removing a statement in FDA's draft regulation to the effect that IRBs had "misinterpreted" the agency's position.

Dr. Chadwick pointed to the problem of "where to stop" in conducting component analysis. He said he understood that IRBs should look at the "package" of procedures and only focus on those that are not minimal risk and done for direct benefit. Dr. Levine stressed again that the National Commission did not envision a documentation of risk for every intervention and said attention should be focused only

on those that may be beyond the threshold. Dr. Nelson said that when he served as IRB Chair he divided procedures by category and documented under which section of the regulations procedures each was approved.

Mr. Forster noted that the analysis of direct benefit of various arms of an intervention is often complicated by consideration of standard of care. He asked whether speakers considered standard of care offered in the placebo arm to be direct benefit. Dr. Nelson said this should not be an issue; rather, the focus should be on the research component. Dr. Levine said the biggest issue in placebo controls was whether or not they involved withholding therapy that is even partially effective. He stressed that risk analysis should include what is *not* being done.

A draft recommendation was drafted and presented by a small group of SACHRP members during a break:

> *SACHRP recommends that FDA and OHRP issue joint guidance, or if that is not feasible, consistent guidance, explaining how to perform component analysis in the application of Subpart D. Such guidance might include:*
>
> 1. *How to apply 50.51(404), 50.53 (406), and 50.52 (405) to controlled trials and specifically to placebo-controlled trials,*
> 2. *How component analysis does or does not apply to social and behavioral research, and*
> 3. *What documentation from the IRB must be or should be included.*
>
> *Furthermore, SACHRP recommends that education and training materials for IRB members and investigators be made available and a communication plan developed.*

Dr. Chadwick asked about expanding the recommendation to apply to other Subparts. Dr. Levine said other Subparts are not inconsistent with the approach taken in Subpart D, and he held that component analysis should apply across the board. Dr. Bierer suggested focusing on Subpart D, where component analysis is integral, for the purpose of the recommendation. It could be revisited to see how it would apply in adult trials at a later time. She noted that it was possible to explain risks and benefits to adults in ways that children cannot understand.

SACHRP members agreed that reference should be made to parental consent and to assent by pediatric subjects.

Dr. Lux, who has served as ex officio for the Environmental Protection Agency, informed SACHRP that this was his last meeting in this capacity. Dr. Bierer thanked him for a "terrific collaborative partnership."

ACTION

SACHRP unanimously approved the following recommendation:

> *SACHRP recommends that FDA and OHRP issue joint guidance, or if that is not feasible, consistent guidance, explaining how to perform component analysis in the application of Subpart D. Such guidance might include:*

1 *How to apply 50.51(404), 50.53 (406), and 50.52 (405) to controlled trials and specifically to placebo-controlled trials*
2 *How component analysis does or does not apply to social and behavioral research,*
3 *How component analysis might impact parental consent and pediatric assent, and*
4 *What documentation from the IRB must be or should be included.*

Furthermore, SACHRP recommends that education and training materials for IRB members and investigators be made available and a communication plan developed.

Attachment A. Recommendations Regarding Oversight of Research Misconduct and Regulatory Noncompliance, As Presented

Over the past few months, SACHRP, both in its own sessions and in those of its Subcommittee on Harmonization, have considered the intersection of the jurisdictions, regulatory processes, and sanctions of the Office for Human Research Protections (OHRP) and the Office of Research Integrity (ORI). As described more fully herein, SACHRP also has noted this jurisdictional and procedural intersection in light of the proposed rule of the Food and Drug Administration relating to possible falsification of data by investigators. 75 Fed. Reg. 7412 (Feb. 19, 2010).

Concerned by our findings in this area, we write at this time to call to the Secretary's attention some significant disharmonies between these sets of procedures that govern (or in the case of the FDA's pending proposal, would govern) noncompliance with regulatory standards relating to research with human subjects. SACHRP asks that these issues be addressed in unified or coordinated guidance from these agencies within the Department of Health and Human Services, or, to the extent necessary, by regulatory amendments.

According to presentations made to SACHRP by ORI representatives, ORI accepts jurisdiction over matters relating to possible fabrication, falsification, or plagiarism in research funded by the Public Health Service (PHS). Of course, alleged fabrication or falsification of data, or plagiarism of previous scholarly work and data may occur in any research, not limited to research with human subjects. In identifying categories of alleged violations that would be included in its jurisdiction, ORI historically has deferred to OHRP in certain matters relating to human subject research, consistent with OHRP's jurisdiction over possible violations of the Common Rule, 45 CFR 46. ORI has typically, for example, deferred to OHRP in relation to, among other matters, allegations of falsified or forged consent forms, failure to obtain informed consent, failure to report unanticipated adverse events, forging an investigator's signature, enrolling subjects who fail to meet eligibility criteria, and protocol deviations of other sorts. At the same time, ORI has reported that it would accept jurisdiction over allegations of substituting one research subject's record for another, changing research records to reflect desired data and results, altering subject eligibility test results, and falsifying dates on screening logs for prospective subjects.

1. Ambiguities of OHRP and ORI Jurisdictions

In its ongoing discussions with ORI and OHRP, SACHRP has presented a series of jurisdictional scenarios that would seem to illustrate that the historic allocation of categories of alleged noncompliance roles between these two agencies may have resulted in inadequate pursuit of significant violations of research integrity standards. Among the scenarios that SACHRP has offered for discussion include:

- An investigator systematically varies a protocol from what was presented to and approved by IRB, and publishes the results; later analysis reveals that results were rendered unreliable by the noncompliance, and publication is withdrawn. Noncompliance could be related to a failure to measure at defined points, or coercion of subjects so intense as to skew survey results. Under current practice, ORI would presumably defer to OHRP in this case, although in fact the investigator has, through noncompliance with human subject protection regulations, adulterated the study data so as to render those data worthless, and not suitable for publication.

- An investigator falsifies informed consent forms in a study in which informed consent has been described in detail in the research protocol approved by the IRB, but study subjects were otherwise treated appropriately. In publication, the human subjects section inaccurately describes the elaborate informed consent process that was described in the protocol and approved by the IRB, but that was in fact not followed by the investigator. The IRB discovers this serious human subject research regulatory deviation, and requires, as a sanction, that the investigator not use the collected data. The study, paid for with significant federal grant funds, is now worthless. At the present time, it appears that ORI might cede jurisdiction of the case to OHRP, even though there has been falsification of documents, with significant harm to research integrity and a waste of federal funds.

- To achieve statistically significant results, an investigator fabricates research data on 50 subjects, and reports enrollment as 100. Only 50 subjects actually enrolled and completed a complicated, lengthy protocol, and the protocol had no direct benefit to the subjects. The investigator combines the fabricated data on 50 fictitious subjects with actual data on the 50 true subjects, and publishes the results. This represents both fabrication of data and the unjustifiable depriving of actual subjects of their time and trouble, with the investigator having offered false promise of scientific benefit for society or any specific population. This research misconduct would also seem to represent a serious violation of human subject research standards. If, under what seems to be customary practice, ORI and OHRP agree that only one of them will accept jurisdiction of the case, it is not clear to SACHRP how such an exclusive allocation would assert the purposes of both the Common Rule and ORI research integrity standards.

- An investigator falsifies eligibility criteria information on enrollment forms for subjects, so that a full complement of subjects can be enrolled quickly. The study is conducted with multiple subjects whose eligibility criteria/enrollment forms were falsified. A research misconduct inquiry process, undertaken under ORI requirements, reveals this. Thereafter, disclosure is made to the IRB, leading to an IRB finding that multiple subjects who were actually ineligible for the study were subjected to serious and harmful research interventions. It appears to SACHRP that this incident of research misconduct also should be viewed as a violation of human subject research standards under 45 CFR 46, and would properly be handled under the jurisdiction of both OHRP and ORI as separate processes or a single coordinated process.

- An investigator fails to report serious and unexpected adverse events, as well as injuries to subjects that should and could have been avoided. Unexpected adverse events and injuries in turn were not reported in FDA submissions, and were not reported in publications. The study publications and FDA submissions erroneously indicate, in fact, that few or no serious adverse events occurred during the study. This FDA violation would also seem to constitute research misconduct and a violation of human subject research standards. It is unclear, however, how

for enforcement purposes, FDA, OHRP, and ORI would interact to assure that the purposes of each office's regulations would be served.

On first impression, it may seem that given limited resources, there has been adequate enforcement, as long as at least one of the HHS offices has accepted jurisdiction over a matter. However, given the differing standards for burdens of proof and sanctions available to the various offices, the ultimate outcomes for very similar violations could vary significantly—from OHRP acceptance of an IRB-designed "corrective action plan," on the one hand, to public censure by HHS and several years' debarment from receipt of any federal funds, on the other.

2. Differences in Processes, Standards and Enforcement

Indeed, the length and formality of processes vary significantly between ORI and OHRP. The relatively informal processes that may be employed by IRBs under the Common Rule tend to be much more rapid than the ORI-mandated processes of inquiry and investigation. Second, the burden of proof of violations and evidentiary standard are undefined under the Common Rule, but are designated as the "preponderance of evidence" under ORI's regulations. Third, OHRP generally enforces Common Rule standards against institutions, under the terms of their FederalWide Assurance (FWA), while ORI and FDA typically impose sanctions against individual investigators rather than research institutions, unless they also find failings in an institution's internal processes. Fourth, ORI processes stress the confidentiality of research misconduct proceedings and the need to protect an investigator's reputation, while Common Rule standards are much more concerned with protection of human subjects than with the peer and public perceptions of an investigator.

Each of these areas of difference could contribute to uneven, or even inadequate, enforcement when a complex factual situation, such as those set forth above, threatens some combination of human subject research noncompliance (OHRP) and research misconduct (ORI). [4]

Further, SACHRP received comments from institutional officials whose internal compliance efforts in regard to human subject research and research misconduct (as defined by ORI) had been vastly complicated by the differences in these offices' regulatory processes and standards, including those relating to burden of proof and confidentiality. Our research institutions appear to be disadvantaged in their compliance efforts by confusion in regard to matters that span ORI, FDA and OHRP jurisdiction, given that IRB and research misconduct proceedings typically are triggered by a common set of events, and that one proceeding can lead rapidly to the commencement of another procedure.

Among the composite scenarios described in presentations to SACHRP by institutional officials have been the following:

- An IRB investigated a situation that arose during a parallel research misconduct proceeding, but IRB findings and penalties (suspension of an investigator from conducting human subjects research for a defined period) long preceded any conclusion reached in the research misconduct process. The IRB made its required report to OHRP, which then replied by accepting the report and posting the information on the OHRP website. Therefore, the human subject violations

[4] SACHRP notes that it would be useful to include FDA procedures, standards and enforcement in this analysis, so that the regulatory processes of FDA could be reconciled with those of OHRP and ORI. To date, however, except for consideration of the recent proposal by FDA to require prompt sponsor reporting of suspicions of falsification of data, SACHRP has not explored with FDA how all of these issues might relate to FDA's own processes and jurisdiction. SACHRP encourages the Department to include FDA in its own analysis of these issues, because matters relating to ORI and OHRP can easily also relate to FDA.

that formed an essential component of the research misconduct, were already determined and information about those violations publicly available, prior to the conclusion of the research misconduct process.

- In parallel proceedings, and closely related fact patterns, an IRB and a research misconduct process led to findings that noncompliance with Common Rule standards had occurred, but research misconduct allegations were not substantiated. The IRB and the research misconduct process reached different conclusions about the basic facts of what had occurred. The project was supported by a PHS grant. The institution therefore had two differing, conflicting sets of fact findings, and was confused about what to report: reporting the IRB findings to the Public Health Service would have been consistent with OHRP and PHS requirements, but would have reflected badly on the investigator's integrity, while respecting the finding that research misconduct had not been substantiated would have preserved the investigator's reputation but would have violated required reporting to the Public Health Service, as grant sponsor.

- An IRB investigated fabrication of informed consent documents and related violations of eligibility criteria for enrollment, and then suspended the protocol, requiring the investigator to notify subjects of the study suspension and of the reasons for the suspension. Although the matter was referred also to the research misconduct inquiry process, subjects and co-investigators were advised of the Common Rule regulatory violations – as was OHRP in an institutional letter reporting the suspension – long before any research misconduct process had been completed. The investigator protested, suggesting that his reputation was being ruined before the confidential misconduct process had even passed the inquiry stage.

- In an attempt to preserve the required confidentiality of the research misconduct process, a research integrity official failed to disclose to the IRB a serious allegation of research misconduct in an ongoing study with human subjects. At the time the allegation was received, there was no indication that the alleged research misconduct could be placing subjects at any increased risk of harm, but the subsequent inquiry and investigation produced evidence that subjects had been placed at increased risk. Had the IRB known these facts (or had the IRB known enough to have initiated its own investigation), the study would likely have been suspended, but the IRB did not learn of the research misconduct allegation until many months after it had been reported to the research integrity official. Ultimately, the investigation process resulted in a finding that research misconduct in fact had occurred; however, by that point, the study had concluded. Subjects had been exposed to risks and inconvenience in a discredited study.

These are only a few examples of the many ways in which applying Common Rule standards and OHRP guidelines can become enormously complex when the allegations also suggest possible research misconduct.

3. Specific Issues Requiring Clarity

Among the specific questions that SACHRP suggests merit official guidance are the following:

- Does a sufficiently credible and specific allegation of misconduct in research involving human subjects qualify as an "unanticipated problem involving risks to subjects or others or any serious or continuing noncompliance" that requires prompt reporting to OHRP?

- How should the IRB, the research integrity officer and the institutional official interact with one another about serious allegations received in which both human subjects and research misconduct issues are implicated? Given regulatory requirements of confidentiality in the research misconduct process,[5] should a research integrity officer advise the institutional official and the IRB of allegations that relate to human subjects protections, and if, so, at what point in the research misconduct process?

- When records and data have been sequestered, as required, in a research misconduct proceeding, what access should an IRB have to those materials, when they are needed for a related IRB inquiry?

- For OHRP reporting purposes, corrective actions, and notification to subjects, what should an IRB do if IRB determinations are made prior to or the determinations differ from final research misconduct findings on the same factual issues?

- To what extent should IRB determinations of serious noncompliance be factored into an institution's responsibility to "protect or restore" the reputation of an investigator who has been cleared of closely related research misconduct allegations?

- How should a research misconduct proceeding treat IRB findings of unsubstantiated noncompliance, when the research misconduct process yields differing determinations on essentially the same evidence? Should it matter to the analysis of this question that the research misconduct process employs a specified standard of proof ("preponderance of the evidence")?

- Should research subjects be informed if and when research misconduct has been conclusively determined in a study in which the subjects participated?

4. <u>FDA Standards and Proposed Mandatory Reporting of Suspected Falsification of Data</u>

SACHRP has not fully explored how standards and processes in suspected noncompliance differ between FDA, on the one hand, and OHRP and ORI on the other. Nevertheless, in many cases of research with human subjects in which professional standards have been compromised, it is entirely possible that concerns would arise, and enforcement action would be possible, under FDA, OHRP and ORI jurisdiction, simultaneously. Therefore, in developing guidance for research institutions, it would

[5] See 42 CFR 93.108(b): "Except as may otherwise be prescribed by applicable law, confidentiality must be maintained for any records or evidence from which research subjects might be identified. *Disclosure is limited to those who have a need to know to carry out a research misconduct proceeding"* [emphasis added].

seem appropriate to include consideration of how FDA jurisdiction, standards, processes and enforcement could interact with those of OHRP and ORI.

Specifically, SACHRP is mindful of the pending proposal by FDA for adoption of rigorous requirements that sponsors (which would include sponsor institutions) report suspicion of falsification of data in clinical investigations, nonclinical laboratory studies, and clinical studies in animals. 75 Fed. Reg. 7412 (Feb. 19, 2010). Under this proposal, a sponsor that "becomes aware of information indicating that any person has, or may have, engaged in falsification of data" in such studies would be required to report this to FDA within 45 days, so that FDA would have an "early alert to potentially serious lapses in subject protection or data integrity," 75 Fed. Reg. at 7416, and would be able to take swift action to abate any threat.

The difficulty with this approach is directly related to the substance of this letter: this "early warning" by sponsors to the FDA has significant implications for, and would interact in complex ways with, existing institutional processes for protecting human subjects and for investigating allegations of research misconduct. FDA actions, if taken quickly in response to such a report, could significantly complicate IRB actions and institutional research misconduct proceedings, in ways that are not completely clear but whose outlines are already suggested by the difficulties in reconciling OHRP with ORI processes and standards. Having a third set of standards that also could apply in these settings would yield additional complexity and confusion, unless regulations and guidance clearly indicate how all three sets of standards might be applied in a coordinated, non-disruptive way.

In light of this pending FDA proposal, the questions raised by SACHRP in this letter are timely indeed, and should be addressed before additional complexity is added to an already confusing regulatory regime. SACHRP's concerns in this regard were, in fact, voiced by multiple institutions and persons that commented on the proposal when it was originally published in the Federal Register, with many comments indicating that a strict reporting FDA standard could wreak havoc on established institutional IRB and research misconduct processes.[6]

Finally, SACHRP notes that some research projects funded by various offices and agencies within HHS may be co-supported by, and/or share professional staff and resources with, research projects funded by other agencies of the United States government. In the process of addressing the issues raised in this letter, HHS may therefore wish to consider how HHS-mandated processes and standards for research misconduct may be inconsistent with the various analogous processes and standards of these other agencies.

[6] See, e.g., *Comments of the Association of American Universities and Council on Governmental Relations on FDA Proposal for Reporting Information Regarding Falsification of Data*, May 19, 2010.

Attachment B. SACHRP Recommendations Regarding Oversight of Research Misconduct and Regulatory Noncompliance, As Approved

Over the past few months, SACHRP, both in its own sessions and in those of its Subcommittee on Harmonization, ***has*** considered the intersection of the jurisdictions, regulatory processes, and sanctions of the Office for Human Research Protections (OHRP) and the Office of Research Integrity (ORI). As described more fully herein, SACHRP also has noted this jurisdictional and procedural intersection in light of the proposed rule of the Food and Drug Administration relating to possible falsification of data by investigators (*75 Fed. Reg. 7412*, February 19, 2010). ***These various regulatory regimes interact in complex ways with existing institutional processes for protecting human subjects, for preserving the reputation of the respondent, and for investigating allegations of research misconduct. Most importantly, the circumstances in which human subjects research may deviate from accepted professional standards do not necessarily respect the fine-grained distinctions between noncompliance under the Common Rule, research misconduct, and violations of FDA regulations. In our deliberations in this area, SACHRP has identified*** some significant disharmonies between these sets of procedures that govern (or in the case of the FDA's pending proposal, would govern) noncompliance with regulatory standards relating to research with human subjects. SACHRP asks that these issues be addressed in unified or coordinated guidance from these agencies within the Department of Health and Human Services, or, to the extent necessary, by regulatory amendments.

According to presentations made to SACHRP by ORI representatives, ORI accepts jurisdiction over matters relating to possible fabrication, falsification, or plagiarism in research funded by the Public Health Service (PHS). Of course, alleged fabrication or falsification of data, or plagiarism of previous scholarly work and data may occur in any research, not limited to research with human subjects. In identifying categories of alleged violations that would be included in its jurisdiction, ORI historically has deferred to OHRP in certain matters relating to human subject research, consistent with OHRP's jurisdiction over possible violations of the Common Rule, 45 CFR 46. ORI has typically, for example, deferred to OHRP in relation to, among other matters, allegations of falsified or forged consent forms, failure to obtain informed consent, failure to report unanticipated adverse events, forging an investigator's signature, enrolling subjects who fail to meet eligibility criteria, and protocol deviations of other sorts. At the same time, ORI has reported that it would accept jurisdiction over allegations of substituting one research subject's record for another, changing research records to reflect desired data and results, altering subject eligibility test results, and falsifying dates on screening logs for prospective subjects.

1. Overlapping Regulatory Regimes of OHRP, ORI and FDA

SACHRP has presented a series of jurisdictional scenarios that would seem to illustrate the ***overlapping nature of noncompliance under the regulatory regimes overseen by OHRP, ORI and FDA.*** Among the scenarios that SACHRP has offered for discussion include:

- *[Deleted first example]*

- An investigator falsifies informed consent forms in a **PHS-funded** study in which informed consent has been described in detail in the research protocol approved by the IRB, but study subjects were otherwise treated appropriately. In publication, the human subjects section inaccurately describes the elaborate informed consent process that was described in the protocol and approved by the IRB, but that was not followed by the investigator. The IRB discovers this serious human subject research regulatory deviation, and requires that the

investigator not use the collected data. The study, paid for with significant federal grant funds, is now worthless. **There** has been falsification of documents, with significant harm to research integrity and a waste of federal funds, **all caused by significant deviations from an IRB-approved protocol.**

- To achieve statistically significant results **in an NIH-funded study**, an investigator fabricates research data on 50 subjects, and reports enrollment as 100. Only 50 subjects actually enrolled and completed a complicated, lengthy protocol, and the protocol had no direct benefit to the subjects. The investigator combines the fabricated data on 50 fictitious subjects with actual data on the 50 true subjects, and publishes the results, **which are then also used to support an FDA submission,** This represents fabrication of data, **deviation from an IRB-approved protocol that is so significant that it has destroyed the integrity of the study,** and **information to the FDA.** This research misconduct would also seem to represent a serious violation of **standards relating to** human **subjects** research **and of FDA regulations.**

  Further, if subsequent studies (for example, the progression to phase II or phase III studies) were premised on inaccurate results in this study, then subjects in the later studies would have been put at unjustifiable risk; the gravity of protocol deviations in this study would thus have been compounded by later reliance on study results, with subjects directly endangered.

- An investigator falsifies eligibility criteria information on enrollment forms for subjects, so that a full complement of subjects can be enrolled quickly. The study is conducted with multiple subjects whose eligibility criteria/enrollment forms were falsified. A research misconduct inquiry process, undertaken under ORI requirements, reveals this. Thereafter, disclosure is made to the IRB, leading to an IRB finding that multiple subjects who were actually ineligible for the study were subjected to serious and harmful research interventions. **This** incident of research misconduct also should be viewed as a violation of human **subjects** research standards under 45 CFR 46.

- **In a study partially funded by NIH, an** investigator fails to report serious and unexpected adverse events that **are directly related to the test article. These serious** and **unexpected** adverse events in turn were not reported in **publications or in subsequent** FDA submissions. The study publications and FDA submissions erroneously indicate, in fact, that few or no serious adverse events occurred during the study. This **course of conduct by the investigator** would seem to constitute **FDA violations**, research misconduct, and a violation of human subjects research standards. [Remainder of paragraph and next paragraph deleted.]

2. Differences in ***Institutional Compliance with*** Processes, Standards and Enforcement

In such cases as those set forth above, processes for pursuing allegations of research misconduct, possible deviations from human subjects research standards, and FDA violations vary significantly. FDA on-site enforcement actions and the relatively informal processes that may be employed by IRBs under the Common Rule tend to be much more rapid than the ORI-mandated processes of inquiry and investigation ***for possible research misconduct.*** Second, the burden of proof of violations and evidentiary standard are undefined under the Common Rule, but are designated as the "preponderance of evidence" under ORI's regulations. Third, OHRP generally enforces Common

Rule standards against institutions, under the terms of their FederalWide Assurance (FWA), while ORI and FDA typically impose sanctions against individual investigators rather than research institutions, unless they also find failings in an institution's internal processes. Fourth, ORI processes stress the confidentiality of research misconduct proceedings and the need to protect an investigator's reputation, while ***FDA operates to enforce regulations of compelling public importance, and while*** Common Rule standards are much more concerned with protection of human subjects than with the peer and public perceptions of an investigator. ***Fifth, in order to establish research misconduct, there must be specific evidence of fabrication, falsification or plagiarism by an individual investigator, while FDA and Common Rule standards focus on violations of and deviations from standards, regardless of investigator intention and regardless of causation that is traceable to any identified individual.*** [Next paragraph deleted.]

Specifically, SACHRP ***has*** received comments from institutional officials whose internal compliance efforts in regard to human ***subjects*** research and research misconduct (as defined by ORI) ***have*** been vastly complicated by the differences in regulatory processes and standards, including those relating to burden of proof and confidentiality. Our research institutions appear to be disadvantaged in their compliance efforts by confusion in regard to matters that span ORI, FDA and OHRP jurisdiction, given that IRB and research misconduct proceedings typically are triggered by a common set of events, and that one proceeding can lead rapidly to the commencement of another procedure.

Among the composite scenarios described in presentations to SACHRP by institutional officials have been the following:

- An IRB investigated a situation that arose during a parallel research misconduct proceeding, but IRB findings and penalties (suspension of an investigator from conducting human subjects research for a defined period) long preceded any conclusion reached in the research misconduct process. The IRB made its required report to OHRP, which then replied by accepting the report and, ***upon receipt of FOIA requests, providing*** the ***report to*** the ***public.*** Therefore, the human subject violations that formed an essential component of the ***potential*** research misconduct, were already determined and information about those violations publicly available, prior to the conclusion of the research misconduct process.

- In parallel proceedings, and closely related fact patterns, an IRB and a research misconduct process led to findings that noncompliance with Common Rule standards had occurred, but research misconduct allegations were not substantiated. The IRB and the research misconduct process reached different conclusions about the basic facts of what had occurred. The project was supported by a PHS grant. The institution therefore had two differing, conflicting sets of fact findings, and was confused about what to report: reporting the IRB findings to ***OHRP and PHS*** would have been consistent with OHRP and PHS requirements, but would have reflected badly on the investigator's integrity; ***at the same time,*** respecting the finding that research misconduct had not been substantiated would have preserved the investigator's reputation but would have violated required reporting to ***OHRP and to PHS,*** as grant sponsor.

- An IRB investigated fabrication of informed consent documents and related violations of eligibility criteria for enrollment, and then suspended the protocol, requiring the investigator to notify subjects of the study suspension and of the reasons for the suspension. Although the matter was referred also to the research misconduct inquiry process, subjects and co-investigators were advised of the Common Rule regulatory violations – as was OHRP in an institutional letter reporting the suspension – long before any research misconduct process had

been completed. The investigator protested, suggesting that his reputation was being ruined before the confidential misconduct process had even passed the inquiry stage.

- In an attempt to preserve the required confidentiality of the research misconduct process, a research integrity ***official at the institution*** failed to disclose to the IRB ***an*** allegation of research misconduct in an ongoing study with human subjects. At the time the allegation was received, there was no indication that the alleged research misconduct could be placing subjects at any increased risk of harm, but the subsequent ***research misconduct*** inquiry and investigation produced evidence that subjects had been placed at increased risk. Had the IRB known these facts (or had the IRB known enough to have initiated its own investigation), the study would likely have been suspended, but the IRB did not learn of the research misconduct allegation until many months after it had been reported to the research integrity official. Ultimately, the investigation process resulted in a finding that research misconduct in fact had occurred; however, by that point, the study had concluded. Subjects had been exposed to risks in a discredited study.

These are only a few examples of the many ways in which applying Common Rule standards and OHRP guidelines can become enormously complex when the allegations also suggest possible research misconduct.

3. Specific Issues Requiring Clarity

Among the specific questions that SACHRP suggests merit official guidance are the following:

- Does a sufficiently credible and specific allegation of misconduct in research involving human subjects qualify as an "unanticipated problem involving risks to subjects or others or any serious or continuing noncompliance" that requires prompt reporting to OHRP?

- How should the IRB, the research integrity officer and the institutional official interact with one another about serious allegations received in which both human subjects and research misconduct issues are implicated? Given regulatory requirements of confidentiality in the research misconduct process,[7] should a research integrity officer advise the institutional official and the IRB of allegations that relate to human subjects protections, and if, so, at what point in the research misconduct process?

- When records and data have been sequestered, as required, in a research misconduct proceeding, what access should an IRB have to those materials, when they are needed for a related IRB inquiry?

- For OHRP reporting purposes, corrective actions, and notification to subjects, what should an IRB do if IRB determinations are made prior to or the determinations differ from final research misconduct findings on the same factual issues?

[7] See 42 CFR 93.108: "Disclosure ***of the identity of respondents and complainants in research misconduct proceedings*** is limited***, to the extent possible***, to those who need to know, ***consistent with a thorough, competent, objective and fair*** research misconduct proceeding, ***and as allowed by law."***

- To what extent should IRB determinations of serious noncompliance be factored into an institution's responsibility to "protect or restore" the reputation of an investigator who has been cleared of closely related research misconduct allegations?

- How should a research misconduct proceeding treat ***an*** IRB ***finding that alleged*** noncompliance ***with Common Rule standards was not substantiated,*** when the research misconduct process yields differing determinations on essentially the same evidence? Should it matter to the analysis of this question that the research misconduct process employs a specified standard of proof ("preponderance of the evidence")?

- ***What considerations should IRBs use in determining whether and how*** research subjects ***should b***e informed if ***falsification or fabrication of data has been identified, or if*** research misconduct has been conclusively determined, in a study in which the subjects participated?

4. Investigation and Sanctions Process for Investigators Accused of Serious Violations of Human Subjects Regulations

As noted previously, OHRP generally enforces Common Rule standards against institutions, while ORI and FDA typically impose sanctions against individual investigators rather than against research institutions, unless they also find failings in an institution's internal processes. SACHRP understands that OHRP does have the authority to refer egregious cases of violations of human subjects regulations in HHS-funded research to the Secretary for consideration of enforcement actions against individual investigators, such as debarment from applying for or benefiting from HHS research funds. However, SACHRP also understands that this authority has never been exercised by OHRP. Furthermore, this enforcement pathway may not formally incorporate due process protections for investigators who are accused of serious and intentional violations of human subjects regulations.

The situation outlined here creates a serious inconsistency in how the Department addresses various ways in which individual investigators may deviate from professional standards of conducting research. On the one hand, the Department has the ability, through ORI, to sanction a PHS-funded researcher who is found, after an ORI process, to have engaged in research misconduct (i.e., fabrication, falsification or plagiarism (FFP)), and through the FDA, to sanction an investigator who violates FDA regulations. On the other hand, it is much less obvious how the Department can, and under what circumstances the Department should, sanction an individual investigator who engages in serious violations of HHS human subjects regulations. This leads to the possibility, for example, that a PHS sponsor such as the NIH might be unaware of an investigator's history of serious and intentional violations of human subjects regulations when considering a grant application from that individual. This apparent gap is difficult to defend, may lead to subject harm, and may jeopardize public trust in the research enterprise should an example of egregious previous violations of human subjects regulations by a PHS-funded investigator come to light.
To address the gap described above, SACHRP recommends that the Department develop a mechanism for investigation of such cases, for imposition of sanctions as indicated, and for communicating the relevant findings to other affected federal agencies when an HHS-funded researcher is accused of serious violations of human subjects regulations. One option might be for OHRP and/or PHS (as a research funder) to develop a mechanism for undertaking such an investigation, for recommending appropriate sanctions, and for developing appropriate communication strategies.

5. FDA Standards and Proposed Mandatory Reporting of Suspected Falsification of Data

[First two sentences deleted.] In developing guidance for research institutions, it would seem appropriate to ***include specific*** consideration of how FDA jurisdiction, standards, processes and enforcement ***may*** interact with those of OHRP and ORI. Specifically, SACHRP is mindful of the pending proposal by FDA for adoption of rigorous requirements that sponsors (which would include sponsor institutions) report suspicion of falsification of data in clinical investigations, nonclinical laboratory studies, and clinical studies in animals. 75 Fed. Reg. 7412 (Feb. 19, 2010). Under this proposal, a sponsor that "becomes aware of information indicating that any person has, or may have, engaged in falsification of data" in such studies would be required to report this to FDA within 45 days, so that FDA would have an "early alert to potentially serious lapses in subject protection or data integrity," 75 Fed. Reg. at 7416, and would be able to take swift action to abate any threat.

The difficulty with this approach is directly related to the substance of this letter: this "early warning" by sponsors to the FDA has significant implications for, and would interact in complex ways with, existing institutional processes for protecting human subjects, ***for preserving the reputation of the respondent,*** and for investigating allegations of research misconduct. FDA actions, if taken quickly in response to such a report, could significantly complicate IRB actions and institutional research misconduct proceedings, in ways that are not completely clear but whose outlines are already suggested by the difficulties in reconciling OHRP with ORI processes and standards. Having a third set of standards that also could apply in these settings would yield additional complexity and confusion, unless regulations and guidance clearly indicate how all three sets of standards might be applied in a coordinated, nondisruptive way.

In light of this pending FDA proposal, the questions raised by SACHRP in this letter are timely indeed, and should be addressed before additional complexity is added to an already confusing regulatory regime. SACHRP's concerns in this regard were, in fact, voiced by multiple institutions and persons that commented on the proposal when it was originally published in the Federal Register, with many comments indicating that a strict reporting FDA standard could wreak havoc on established institutional IRB and research misconduct processes.[8]

Finally, SACHRP notes that some research projects funded by various offices and agencies within HHS may be co-supported by, and/or share professional staff and resources with, research projects funded by other agencies of the United States government. In the process of addressing the issues raised in this letter, HHS may therefore wish to consider how HHS-mandated processes and standards for research misconduct may be inconsistent with the various analogous processes and standards of these other agencies.

[8] See, e.g., *Comments of the Association of American Universities and Council on Governmental Relations on FDA Proposal for Reporting Information Regarding Falsification of Data*, May 19, 2010.

Attachment C: Recommendations on Protocol Deviations, As Approved

Recommendation on Protocol Deviations

A problematic area in human subject protection is the wide divergence among institutions, sponsors, investigators and IRBs regarding the definition of and the procedures for reviewing protocol deviations.

Focus of the Recommendation

In virtually every research study departures occur from the procedures set forth in the IRB-approved protocol. Various terms are used to describe these departures, including "protocol deviations," "protocol violations," "protocol variances," and "non-compliance." For the purposes of this recommendation, such departures shall be herein referred to as "protocol deviations." Protocol deviations occur for a variety of reasons, such as an investigator's decision to deviate from the protocol, the subject's lack of adherence to the protocol, or external/environmental factors (e.g., severe weather or holidays) that change the performance of a protocol. Some protocol deviations are anticipated and/or intentional; others are not. Some protocol deviations are known or identified before they occur; others are only discovered to have occurred after the fact. The HHS and FDA regulations and guidance are inconsistent in addressing protocol deviations, and even among the various FDA regulations and guidance documents there are inconsistencies. However, as noted below in its central recommendation, SACHRP believes that FDA and OHRP can provide guidance to clarify their currently existing positions on this issue.

This recommendation specifically addresses three types of deviations:

- Deviations that occur because an investigator, research staff or other party involved in the conduct of research intentionally decides to deviate from the approved protocol.
- Deviations from the protocol that are identified before they occur, but cannot be prevented.
- Deviations from the protocol that are discovered after they occur.

Each of these deviations is defined and examples are provided is sections II, III, and IV below. Section V contrasts two other activities from the three types of deviations. These other two activities are:

- Deviations from the protocol performed to eliminate apparent immediate hazards to the subject in compliance with 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(4).
- Changes in research made in compliance with 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(3) and (a)(4).

Both of these activities are outside of the scope of this recommendation.

Section VI provides SACHRP's secondary recommendations regarding the three types of deviations.

I. Current FDA and OHRP Interpretation, and SACHRP's Central Recommendation

The HHS and FDA regulations are inconsistent in addressing protocol deviations. In addition, among the various FDA regulations and guidance there are inconsistencies. However, FDA and OHRP have each indicated in various formats that intentional protocol deviations are changes in research that need prior IRB review and approval. SACHRP's central recommendation is that FDA and OHRP publish a clear statement of their positions regarding intentional protocol deviations. The following are the essential statements of the current FDA and OHRP positions on protocol deviations. (See Appendices I and II for additional background information on existing regulations and guidance.)

FDA Center for Device and Radiologic Health (CDRH):

FDA device regulations explicitly address protocol deviations. 21 CFR 812.150 requires:

> (a) Investigator reports. An investigator shall prepare and submit the following complete, accurate, and timely reports:
> ...
> (4) Deviations from the investigational plan. An investigator shall notify the sponsor and the reviewing IRB (see §56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical wellbeing of a subject in an emergency. ... Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB [approval] in accordance with §812.35(a) also is required.

FDA Center for Drug Evaluation and Research (CDER):

FDA drug regulations do not explicitly address protocol deviations. However, the issue is directly addressed in the FDA "Compliance Program Guidance Manual, Program 7348.811, Chapter 48 – Bioresearch Monitoring, Clinical Investigators and Sponsor-Investigators, December 8, 2008." The manual states:

> Protocol deviations. A protocol deviation/violation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. A protocol deviation could be a limited prospective exception to the protocol (e.g. agreement between sponsor and investigator to enroll a single subject who does not meet all inclusion/exclusion criteria). Like protocol amendments, deviations initiated by the clinical investigator must be reviewed and approved by the IRB and the sponsor prior to implementation, unless the change is necessary to eliminate apparent immediate hazards to the human subjects (21 CFR 312.66), or to protect the life or physical well-being of the subject (21 CFR 812.35(a)(2)), and generally communicated to FDA. "Protocol deviation" is also used to refer to any other, unplanned, instance(s) of protocol noncompliance. For example, situations in which the investigator failed to perform tests or examinations as required by the protocol or failures on the part of study subjects to complete scheduled visits as required by the protocol, would be considered protocol deviations. Determine whether changes to the protocol were:
>
> i. Documented by an amendment, dated, and maintained with the protocol;
> ii. Reported to the sponsor (when initiated by the clinical investigator); and
> iii. Approved by the IRB and FDA (if applicable) before implementation (except when necessary to eliminate apparent immediate hazard(s) to human subjects).

Office for Human Research Protections (OHRP):

OHRP has not issued written guidance on protocol deviations. However, OHRP's unwritten position is that all intentional protocol deviations are changes in research that need prior IRB review and approval before implementation.

At the current time, much of the regulated community is unaware of these positions. SACHRP's central recommendation is that FDA and OHRP issue either joint guidance, or if that is not feasible, separate consistent guidance clearly outlining these positions.

The remainder of this letter contains discussion points and references for FDA and OHRP consideration, and minor recommendations on specific points.

II. Intentional Protocol Deviations

The first focus of this recommendation is deviations that occur because an investigator, research staff or other party involved in the conduct of research intentionally decides to deviate from the approved protocol. Examples of such intentional protocol deviations include the following types of cases:

- Lab criteria: One test is out of range for a benign reason (increased alkaline phosphatase, LDH or SGOT in a runner, or increased bilirubin in a person with Gilbert Syndrome). The investigator decides to enroll the subject despite the out-of-range lab criteria.

- Age criteria: The criteria includes an age requirement of 20-60 years of age, but a potential subject turned 61 a week before screening. The investigator decides to enroll the subject despite being outside of the age range.

- Payment: The protocol specifies that subjects will be paid twenty dollars per visit. To compensate for higher expenses, the investigator decides to pay certain subjects more than other subjects.

- Timing of study visit: At the time of enrollment, the investigator realizes that due to a planned vacation the subject will miss one out of 12 regularly scheduled two-week study visits. The investigator decides to enroll the subject despite this knowledge.

- Timing of washout: A planned vacation interferes with a washout period. Shortening the wash-out period from 14 to 12 days will allow the subject to be enrolled. The investigator decides to enroll the subject with a 12-day washout.

- Pre-treatment exceeded: Protocol entry criteria specify that only a certain amount of pre-treatment of disease is acceptable. A potential subject has exceeded it to a minimal extent. The investigator enrolls the subject despite knowledge of the extent of the pre-treatment.

- Changes to survey instrument: In a behavioral study utilizing a questionnaire, the investigator realizes that two of the questions would work better in reverse order. The investigator re-orders the questions without IRB approval.

In these situations, the investigator or another party decides to deviate from the protocol. Sometimes these intentional protocol deviations are a one-time event. Other times they lead to the implementation of a permanent change to the protocol or other research documents. These intentional protocol deviations may or may not adversely affect the safety, rights and welfare of the research subject, and they may or may not adversely affect the scientific validity of the research.

III. Protocol deviations that are identified before they occur, but cannot be prevented

The second topic of focus for this recommendation is deviations from the protocol that an investigator, research staff and/or other party involved in the conduct of the research are able to identify before they occur, but cannot prevent from occurring. An example is a research subject who is on a business trip and calls the investigator to announce that she is stuck in a snow storm and cannot be at a study visit scheduled for the next day. The investigator knows in advance that the deviation will occur, but it is not under the investigator's control, and it is not the investigator's intent to deviate from the protocol. (See point V.5 below).

IV. Protocol deviations that are discovered after they occur

The third topic of focus for this recommendation is deviations from the protocol that occur because an investigator, research staff and/or other party involved in the conduct of the research deviate from the protocol unintentionally, and such deviations are not identified until after they occur. Examples include an investigator's accidental failure to perform a protocol-required physical, a subject's failure to self-administer or incorrectly administer the test agent, or a coordinator's accidental failure to perform a protocol-required blood test on subjects. These deviations from the protocol were not planned nor intended. These types of deviations must be analyzed upon discovery such that a determination may be made as to the root cause of the deviation, and whether or not such a deviation(s) constitutes an unanticipated problem involving risks to subjects or others and/or constitutes serious or continuing non-compliance.

V. Protocol deviations to eliminate apparent immediate hazards and IRB-approved changes in research

The three protocol deviations described in Sections II-IV that are the focus of this recommendation need to be contrasted from deviations to eliminate apparent immediate hazards and from IRB-approved changes in research. Both of these activities are already addressed in the regulations and IRBs are required to have written procedures addressing these activities.

Deviations from the protocol performed to eliminate apparent immediate hazards to the subject in compliance with 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(4): These differ from the protocol deviations as described in the examples above in that these types of deviations are performed in reaction to a perceived hazard, such as the occurrence of an unexpected serious adverse event. They are intentional, but they are done to prevent harm to subjects in a time-sensitive situation, as specifically allowed by the regulations. Thus, they are distinct from the intentional deviations that are the focus of this recommendation.

IRB approved changes in research under 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(3) and (a)(4): In addition, the protocol deviations that are the focus of this recommendation also need to be

contrasted from IRB-approved changes in research. If an intentional protocol deviation is implemented with appropriate review and approval by an IRB and, when applicable, by the sponsor, then it is a change in research as allowed under the regulations at 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(3) and (a)(4) rather than a protocol deviation. If it is implemented without such review and approval, then it is an intentional protocol deviation.

VI. - Recommendations

Consistent with section I above, SACHRP recommends that OHRP and FDA issue a joint guidance, or if that is not feasible consistent guidance, on the procedures for handling protocol deviations. The guidance should **ensure the adequate** protection of subject safety and integrity **of the study while taking into account the burden on investigators and IRBs.** The following points should be addressed:

1. The guidance should reinforce the responsibility of investigators and research staff to follow the written protocol as provided by the sponsor and approved by the IRB. Strict adherence to the protocol is more likely to protect human subjects and preserve the integrity of the data and research.

2. The guidance should encourage sponsors and investigators to develop protocols that include flexibility in research methods where possible without adversely affecting subject safety or science. Flexibility that is built into the protocol will reduce the number of changes that have to be reviewed by the IRB and should reduce the number of incidents of deviations and non-compliance by investigators.

3. The guidance should require that permanent changes to protocols be submitted to the IRB as changes to previously approved research for review and approval prior to initiation. This recommendation is consistent with 45 CFR §46.103(b)(4) and 21 CFR §56.108(a)(4). If a modification is minor, it may be reviewed by the expedited procedure or the convened IRB. When applicable, such changes should also have prior sponsor review and approval. Permanent changes to the protocol that are administrative in nature and have no material effect on the regulatory criteria for approval of research, such as a change in telephone number, may be handled outside the IRB process (i.e., by IRB staff). This is consistent with Section E of the current OHRP "Guidance on IRB Approval of Research with Conditions," which states the following: "*Protocol corrections that are only administrative in nature (e.g., correction of typographical and spelling errors in the protocol) would not need additional IRB review because OHRP does not consider such corrections to be changes to the research.*"

4. The guidance should also address one-time intentional protocol deviations that are not intended as a permanent change to the protocol. The guidance should state that these deviations are changes to the research that require IRB review and approval, and when applicable approval by the sponsor, before the investigator may implement them. These deviations will commonly qualify for expedited review by the IRB. This is SACHRP's central recommendation, as noted above.

5. The guidance should address the administrative procedures and regulatory status when investigators implement one-time intentional protocol deviations without IRB approval. The guidance should address whether this always constitutes non-compliance with the IRB

regulations that must be reported to the IRB. The IRB should determine whether reported intentional protocol deviations affect the criteria for approval of research found at 45 CFR §46.111 and 21 CFR §56.111, and evaluate such deviations according to the IRB's policies and procedures for handling non-compliance and considering whether the deviation constitutes an unanticipated problem involving risks to subjects or others. For research under FDA regulations, the sponsor should also be notified and evaluate the deviation according the sponsor's policies and procedures for handling non-compliance. The agencies should consider whether the guidance should take an approach similar to that in the FDA guidance "Adverse Event Reporting to IRBs" and the OHRP guidance "Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events."

6. The guidance should explicitly distinguish the three types of protocol deviations described in Sections II-IV above. The guidance should also distinguish the three types of deviations from deviations to eliminate apparent immediate hazards and from IRB-approved changes in research.

7. The guidance should specifically address administrative procedures and regulatory status of *deviations from the protocol that are identified before they occur, but cannot be prevented*. The guidance should also contrast those procedures and regulatory status from the procedures and regulatory status for intentional protocol deviations. The investigator should evaluate whether these types of protocol deviations are an unanticipated problem involving risks to subjects or others that needs to be promptly reported to the IRB. Because these protocol deviations are identified before they occur but cannot be prevented, it will usually not be appropriate to submit these deviations to the IRB for prior review and approval as a change in research for two reasons. First, the IRB may decide not to approve the deviation, and second, the IRB may not be able to review the reported deviation prior to its occurrence. Both of these circumstances leave the investigator in the position of not having IRB approval to implement a deviation that the investigator cannot prevent. For research under FDA regulations, the investigator should also inform the sponsor immediately, and the sponsor should also evaluate these protocol deviations as part of its monitoring duties, and take any necessary actions. The agencies should consider whether the guidance should take an approach similar to that in the FDA guidance "Adverse Event Reporting to IRBs" and the OHRP guidance "Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events."

8. The guidance should specifically address administrative procedures and regulatory status of *deviations from the protocol that are discovered after they occur*. The guidance should also contrast those procedures and regulatory status from the procedures and regulatory status for intentional protocol deviations. For research under FDA regulations, the sponsor should also evaluate these protocol deviations as part of its monitoring duties and take any necessary actions. The agencies should consider whether the guidance should take an approach similar to that in the FDA guidance "Adverse Event Reporting to IRBs" and the OHRP guidance "Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events." It will be particularly important for the agencies to balance the burden on investigators and IRBs versus the protection of subject safety and scientific integrity when considering this issue.

9. The guidance should state that IRBs need written policies and procedures addressing the three types of protocol deviations described in Sections II through IV above. The guidance should

highlight any areas where IRBs may exert flexibility in defining and determining which changes must be reported to them. For purposes of clarity, the guidance should also explicitly distinguish the two types of protocol deviations outlined in Section V above.

10. SACHRP recognizes that many institutions and IRBs currently do not have policies and procedures in place for reporting and/or handling the three types of protocol deviations described above. The issuance of guidance that only addresses points #3 - #9 above is likely to significantly increase the burden on IRBs. Thus, it is important that there is appropriate emphasis placed on points #1 and #2 above, both in guidance for IRBs, education for investigators, and through dissemination of best practices. For example, it would be extremely helpful to the research community for FDA and OHRP to each identify and publish, in a consistent manner, examples of how to incorporate flexibility into protocols, education programs that help increase compliance of investigators, and models IRBs can use to manage protocol deviations.

Attachment D: Recommendations on Applicability of FDA Regulations, As Approved

Recommendation on Applicability of FDA Regulations
for IRBs (21 CFR 56) and Informed Consent (21 CFR 50)

INTRODUCTION

The HHS regulations regarding human subject protection at 45 CFR 46 differ in limited but significant ways from the FDA regulations regarding human subject protection at 21 CFR 50 and 56. When a research activity is governed by both sets of regulations, then there are certain regulatory provisions that are allowable under 45 CFR 46 that are not allowable under 21 CFR 50 and 56, and thus cannot be applied to the research. The most commonly encountered of these regulatory provisions are the application of the exempt research categories at 45 CFR 46.101(b)(1) through (b)(6), the provision for waiver of consent at 45 CFR 46.116(d), and the provision for a waiver of documentation of consent found at 45 CFR 46.117(c)(1). There is considerable difference in opinion and practice among IRBs, investigators, institutions and sponsors as to when the FDA regulations apply to a research project. To use a common example, an investigator wishes to conduct a retrospective record review of medical records to determine whether drug X had a better outcome than drug Y for arthritis. Some IRBs will consider this to be non-FDA regulated research that is exempt from IRB review and informed consent based on HHS regulation 45 CFR 46.101(b)(4). Other IRBs will consider this to be non-FDA regulated research that needs IRB review but qualifies for a waiver of consent. Finally, a third set of IRBs will determine that this is an FDA regulated clinical investigation that requires IRB review and informed consent under 21 CFR Parts 50 and 56. This is not uncommon, and there are many such examples, as discussed below. OHRP maintains a registration system for IRBs that conduct either HHS funded or supported research or FDA regulated research. If an IRB reviews both types of research, then it must register with both agencies using that system. As of February 3, 2012, there are 2,308 IRBs that are registered with both OHRP and FDA. All of these IRBs face this issue of determining regulatory applicability on a regular basis.

Therefore, SACHRP recommends the issuance of guidance that will provide regulated parties with objective criteria for determining when a research project is under FDA jurisdiction. As represented in the Venn diagram in Appendix II of this recommendation, the goal of this guidance is to clarify the bottom intersecting line, which represents the overlap between FDA and HHS jurisdiction.

OHRP has existing guidance that outlines the steps of analysis as to the level of IRB oversight required of research (http://www.hhs.gov/ohrp/policy/checklists/decisioncharts.html). In summary, that guidance states that the proper analysis under the HHS regulations is:

- Is the activity research?
- Is the activity research involving human subjects?
- Is the activity research that is exempt under 45 CFR 46.101(b)(1) through (6)?
- Is the activity research that can be reviewed through expedited procedures?
- Is the activity research that requires review by a convened IRB?

However, much research is also potentially under FDA jurisdiction. Thus, IRBs could use similar guidance from FDA regarding the definitions of clinical investigation and human subject under the FDA regulations. Ideally, this guidance could be combined with current OHRP guidance on how to determine the status of research under the Common Rule, so that the many IRBs that are registered with both OHRP and FDA would have a single source of guidance on this difficult issue. The result of such guidance would be increased consistency among IRBs and other regulated parties, and subsequently reduced administrative burden on the research community. In addition, if HHS moves forward with the implementation of a Notice of Proposed Rule Making (NPRM) to change the human subject protection regulations, this guidance will provide important public input to OHRP and FDA to proactively consider the relationship between the two sets of regulations and provide clarity on these and similar issues of inconsistency that arise.

RESOLUTION THROUGH GUIDANCE CLARIFYING REGULATORY DEFINITIONS

SACHRP believes that the source of much of the variability of interpretation of the applicability of the FDA regulations stems from the fact that FDA regulations for informed consent (21 CFR Part 50), IRBs (21 CFR Part 56), investigational drugs (21 CFR Part 312), and investigational devices (21 CFR Part 812) contain three different definitions of "human subject," four different definitions of "clinical investigation," and four different definitions of "study article" or its equivalent. These different definitions are provided in Appendix I. It is unclear to the regulated community how to interpret these different definitions, to whom each definition applies, and how the different definitions interact. For instance, it is not clear whether the definitions of "clinical investigation" in 21 CFR Part 50 and 56 are narrower or broader in scope than those in Parts 312 and 812, and when each definition is applicable.

Because these different definitions exist within the FDA regulations, it is difficult to use the same pattern for an algorithm of when the FDA regulations apply. Such an algorithm would follow this order:

- Is the activity a clinical investigation?
- Is the activity a clinical investigation involving human subjects?
- Is the activity exempt under 21 CFR 56.104(a) through (d)?
- Is the activity a clinical investigation that can be reviewed through expedited procedures?
- Is the activity a clinical investigation that requires review by a convened IRB?

If FDA were able to create and publicize an algorithm of this nature, it would resolve many of the issues noted above. SACHRP offers the following thoughts on this issue.

FDA should clarify the interpretation of "clinical investigation" based on the regulatory definitions found in 21 CFR 50, 21 CFR 56, 21 CFR 312, and 21 CFR 812. Each of these four regulations provides a different definition, and it would be very useful to the regulated community if FDA would provide guidance on how these definitions should be interpreted used vis a vis each other and as a whole.[9]

[9] As a model, FDA may wish to consider the May 2011 FDA Draft Guidance for Clinical Investigators, Industry, and FDA Staff on Financial Disclosure by Clinical Investigators, in which the FDA included in the FAQ section questions such as: "How does the definition of 'clinical investigator' in the financial disclosure regulation (21 CFR part 54) relate to the definition in the IND regulations (21 CFR part 312)?" and "How does the definition of 'clinical investigator' in the

SACHRP notes that the definition of a clinical investigation in 21 CFR Part 56 appears to be the broadest of the four definitions. FDA may find it useful to clarify that Part 56 is the broadest of the definitions and encompasses the other three definitions, and then use it as a platform to provide guidance to the regulated community on the definition of a clinical investigation. For instance, the definition of the term "clinical investigation" in Part 56 says it is an experiment in the broadest sense, and that it is synonymous with terms research, clinical research, clinical study, study, and clinical investigation. Therefore, these terms cannot readily be used to differentiate whether an activity is or is not regulated by FDA under 21 CFR Part 56. FDA may find it useful to clarify this point if in fact there are relevant distinctions between the terms that the regulated community could use to determine whether a given research activity is under FDA jurisdiction.

Two additional criteria in 21 CFR Part 56 that appear critical in determining whether a clinical investigation is regulated by FDA is that the clinical investigation is 1) subject to requirements for prior submission to the FDA under section 505(i) or 520(g) of the Food Drug and Cosmetic Act or 2) the clinical investigation is not subject to requirements for prior submission to the FDA under these sections of the Food, Drug and Cosmetic Act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit. It appears that if the investigator or sponsor must submit the data to FDA, or intends to submit the data to FDA, or FDA might inspect the data, then the clinical investigation (research, study, etc) is regulated by FDA under 21 CFR 56. The "held for inspection" condition seems to be particularly broad and the field would benefit from clarification of this and the other criteria.

FDA should clarify the definition of the terms "involves" and "involving" as they are used in the four definitions of a clinical investigation. FDA could clarify whether a test article has to be physically used in the research activity for it to be considered an FDA regulated clinical investigation, or whether alternatively the study can "involve" a test article merely by studying existing data, such as medical records, about the use of the product. This point would help to clarify whether retrospective medical records reviews should be considered to be FDA regulated clinical investigations.

Another difference between the definitions is that under 21 CFR Part 312 any use of a drug, except for the use of a marketed drug in the course of medical practice, is a clinical investigation. However, under 21 CFR Part 812 there is only a clinical investigation when the purpose is to study the safety or effectiveness of the device. FDA should clarify how these two different definitions should be interpreted, particularly as they interact with the definitions of "clinical investigation" in 21 CFR Parts 50 and 56.

In order to provide FDA with a starting point in considering this approach, SACHRP provides the following recommendations on the interpretation of the regulatory definitions:

1. FDA should issue guidance stating that the definition of a clinical investigation at 21 CFR Part 56.102(c) is the broadest statement of FDA's interpretation of a clinical investigation, and encompasses the definitions of a clinical investigation in Parts 50, 312, and 812. As such, IRBs and investigators should use the definition in Part 56 for determinations of whether a given project meets the definition of a clinical investigation.

financial disclosure regulation (21 CFR part 54) relate to the definition in the medical device regulations (21 CFR part 812)?" This type of comparison is very useful.

2. FDA should clarify that even though Part 56 states that "The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part," in fact the definition of research at 45 CFR 46.102(d) is a completely distinct regulatory definition that is not synonymous with the definition of a clinical investigation.

3. FDA should clarify the clause in 21 CFR Part 56.102(c) that states that a clinical investigation, "either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit." FDA should clarify whether this clause causes retrospective record reviews, interviews and questionnaires to become FDA regulated clinical investigations if the intent is to submit the data to FDA or hold the data for FDA inspection. SACHRP recommends that FDA clarify that retrospective record reviews, even when regarding the safety and efficacy of a study article, do not qualify as FDA-regulated clinical investigations. If FDA were to interpret the definition of a clinical investigation such that any retrospective records review involving a regulated study article is a clinical investigation, and therefore that consent is required, much research would not be possible to conduct due to the inability to obtain consent, and the creation of medical knowledge would be significantly curtailed.

4. FDA should clarify the definitions of the terms "involves" and "involving," as they are used in the definition of a clinical investigation in 21 CFR Part 56, related to whether the data will be submitted to FDA or held for FDA inspection, as described in the recommendation above.

5. **FDA should clarify whether the definition of human subject should include consideration of whether or not the data are identifiable. If a link is not maintained, or there is only a one-way link, then perhaps the humans would not be subjects under the FDA definition of a human subject. If a link is maintained, at what point do they become human subjects under the FDA definitions?**

6. Finally, we believe that FDA should further publicize that the definition of "human subject" is limited to living individuals, and does not include dead individuals. The recent March 2011, FDA guidance entitled "Exception from Informed Consent Requirements for Emergency Research" clarified this issue, but if FDA provides guidance on the definition of a clinical investigation, it would also be a practical location to provide better public visibility of this FDA interpretation.

RESOLUTION THROUGH GUIDANCE ON SPECIFIC ISSUES

As an alternate approach to issuing guidance clarifying the regulatory definitions of clinical investigation, human subject, and study article, as discussed above, FDA may find it more practical

and useful to issue guidance on specific examples instead. SACHRP therefore provides the following specific issues and cases that cause confusion as to whether they are FDA regulated clinical investigations.

Retrospective Record Reviews

There is great diversity of opinion among the regulated community as to whether retrospective records reviews are or are not FDA regulated clinical investigations. These retrospective reviews can involve a variety of source data, such as patients' medical records, insurance company records, and publicly available sources such as the Centers for Disease Control (CDC) Death Index. Depending on how the data is collected and recorded, such research may qualify as exempt from the requirements of 45 CFR 46 under the exemption at 46.102(b)(4), may qualify as research not including human subjects under the OHRP "Guidance on Research Involving Coded Private Information or Biological Specimens," or may qualify for a waiver of informed consent under 45 CFR 46.116(d). However, if the research qualifies as an FDA regulated clinical investigation, then IRB review is required and consent cannot be waived. The practical effect of applying FDA jurisdiction to these studies means that many of them would become impossible or impractical to conduct due to the requirement for informed consent. FDA should issue guidance clarifying whether, and if so, under what circumstances retrospective record reviews qualify as FDA regulated clinical investigations.

SACHRP provides the following recommendation:

1. FDA should issue guidance clarifying when, if ever, retrospective record reviews qualify as an FDA-regulated clinical investigation. SACHRP recommends that FDA clarify that retrospective record reviews, even when regarding the safety and efficacy of a study article, do not qualify as FDA-regulated clinical investigations. The guidance should supply a clear rationale so that regulated entities can apply that rationale to specific cases. Furthermore, SACHRP recommends that FDA establish a standard that strikes the best balance for the public good by promoting the discovery and availability of useful medical knowledge while to the extent necessary providing FDA with control over claims of safety and efficacy of FDA regulated products.

Collection of Data for Purposes other than Establishing Safety and Efficacy of Products

FDA should clarify when the use of data generated as part of medical practice is a "clinical investigation." For example, institutions and physicians often implement quality improvement activities that are intended to improve the quality of patient care, and collect patient or provider data regarding the implementation of the practice for clinical, cost analysis, or administrative purposes. FDA should clarify whether such activities could ever qualify as clinical investigations, and if so, what the determining criteria would be.

SACHRP provides the following recommendation:

1. FDA should issue guidance clarifying that collecting or using medical data for purposes other than establishing the safety and efficacy of test articles is not an FDA regulated activity. Examples provided by FDA should include cost effectiveness and quality improvement.

Drug and Device Registries

FDA should provide guidance clarifying when, if ever, drug and device registries qualify as FDA-regulated clinical investigations, and provide the relevant criteria that cause a registry to be FDA regulated. Possible criteria that might be addressed include the identity of the individual or entity that establishes and maintains the registry. The guidance should supply a clear rationale so that regulated entities can apply that rationale to specific cases.
SACHRP provides the following recommendation:

1. FDA should issue guidance clarifying **whether** prospective registries used to collect data regarding the safety and efficacy of FDA regulated test articles are FDA regulated clinical investigations, **particularly when** the study article is not prescribed or used as a result of the existence of the registry. FDA should consider whether certain types of registries, such as registries designed to collect data on fetal exposure to approved drugs through the mother's use during pregnancy, in which the data is collected through voluntary reporting by the physician or the mother, should be considered FDA-regulated clinical investigations, as this data collection cannot be effectively conducted under FDA regulations due to the difficulty of obtaining informed consent.

Risk Evaluation and Mitigation Strategies
FDA should provide guidance clarifying whether and when risk evaluation and mitigation strategies qualify as FDA regulated clinical investigations. [AJ will state the problem]
SACHRP provides the following recommendation:

FDA should issue guidance clarifying that risk evaluation and mitigation strategies are not FDA regulated clinical investigations, unless the study article is prescribed or used as a result of the existence of the risk evaluation and mitigation strategy.

Training Activities
Training activities also often raise questions of FDA jurisdiction. These training activities may involve medical providers or subjects. It would be useful if FDA provided guidance regarding various training activities clarifying whether or not FDA considers the training activities to be clinical investigations:

a. Research to evaluate the effects of training on the administration or use of test articles such as drugs and devices.
b. Training activities regarding regulated products that are mandated by FDA.
c. Training on how to use a device or drug.

SACHRP provides the following recommendation:

FDA should issue guidance clarifying that training activities that are conducted as part of an FDA regulated clinical investigation fall within the FDA regulated investigation. However, training activities that occur separately from an FDA regulated clinical investigation are not, in and of themselves, a clinical investigation unless they involve use of a test article, a human subject, and data

are going to be submitted to FDA or held for FDA. Therefore, an IRB can apply the exemption at 45 CFR 46.102(b) to such training activities if appropriate.

Interviews and Questionnaires

FDA should issue guidance on whether interviews and questionnaires that are administered to medical providers and subjects are FDA regulated clinical trials when they are separate from a clinical investigation. When interviews and questionnaires are administered as part of clinical investigation, they fall within the scope of that investigation. However, sponsors or other parties at times wish to administer interviews or questionnaires separately from a clinical investigation.

SACHRP provides the following recommendation:

FDA should issue guidance clarifying that interviews and questionnaires that are administered to medical providers and subjects separate from FDA regulated clinical trials are not by themselves FDA regulated clinical investigations unless the interview/questionnaire also involves the use of the test article, a human subject, and the data will be submitted to FDA or held for FDA **inspection**. Therefore, an IRB can apply the exemptions at 45 CFR 46.102(b) to such interviews and questionnaires if appropriate.

Studies of Surgical Techniques

An issue of confusion among IRBs is the applicability of FDA regulations to studies of surgical techniques. It is commonly stated that FDA does not regulate surgery, including in FDA's guidance entitled "Available Therapy," which states, "Some confusion has arisen regarding whether available therapy refers only to products approved by FDA for the use in question, or whether the term could also refer to products used off-label or to treatments not regulated by FDA, such as surgery."[10] FDA should clarify when a study of a surgical technique is or is not a device study. Because all surgery involves the use of at least one, and often dozens, of devices, it is either the case that all research on surgical techniques is FDA-regulated device research, or there is some criteria by which some research on surgical techniques does not qualify as device research. Also, if FDA determines that some or all research on surgical techniques does qualify as device research, it would be helpful if FDA guidance provided criteria for determining which devices being used in a given study of surgical technique are the devices for which the IRB must make appropriate regulatory device findings. Surgery often involves dozens of devices, including oximeters, scalpels, sutures, chest spreaders, heart-lung bypass, IV pumps, etc. It would be burdensome for IRBs and investigators to collect the labeling for each of these devices to determine the regulatory status, particularly in multi-site studies because different investigators would very often be using different oximeters, scalpels, etc.

SACHRP provides the following recommendations:

FDA should issue guidance clarifying that studies of surgical techniques are only clinical investigations of devices when the study evaluates the safety or efficacy of the device. If the study is only to test the new technique and not the device, then it falls outside of the device regulations.

Studies of Devices Intended to Obtain Physiologic Data as Opposed to Information About the Safety and Efficacy of the Device

FDA should clarify that the use of a medical device (e.g., an MRI in behavioral and social science research) when the purpose of the study is to obtain basic physiologic information, rather than to test the safety or effectiveness of the device, is not a clinical investigation.

[10] online at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126586.htm:

SACHRP provides the following recommendation:

FDA should clarify that the use of a medical device to obtain basic physiologic information, as opposed to obtaining data regarding the safety or effectiveness of the device, is not a clinical investigation.

CONCLUSION

SACHRP considers the issues presented in this recommendation to be very important. The current lack of clarity of the applicability of FDA regulations causes IRBs, investigators, institutions, and sponsors to apply the FDA regulations inconsistently, causes extensive unnecessary administrative burden and regulatory uncertainty, and may place unnecessary restrictions on valuable research. SACHRP hopes that FDA, OHRP, OCR and other agencies that have adopted the Common Rule will work together to enhance the human subject protection system by addressing these issues.

Attachment E: Recommendations Regarding Individual Patient Treatment Use Protocols, As Approved

SACHRP Recommendations on **Single Patient** Treatment Use

At the SACHRP meeting of October 4, 2011, FDA representatives asked SACHRP to provide feedback to FDA on several questions regarding treatment use of investigational **drugs/biologics** for individual patients, as allowed by 21 CFR 312.305 and 312.310. The representatives noted that FDA continues to hear from individual patients, caregivers, IRB members, and health care professionals that the administrative burdens associated with IRB review of expanded access are onerous and diminish its practicality, negatively impacting access to investigational drugs for treatment under expanded access protocols, particularly single patient treatment access protocols. The problem is particularly acute for physicians and patients that seek expanded access outside of institutional settings with an internal IRB.

The questions FDA asked included:

- What is the Committee's experience with IRB reviews of expanded access protocols?
- How quickly are they reviewed?
- Is there a charge to the individual?
- Are expanded access protocols able to be scheduled ahead of studies already on the calendar?
- Does providing for something like expedited IRB review seem a reasonable solution, based on the problem cited?
- If a reduction in the number of IRB members to approve an expanded access protocol is satisfactory to the Committee, does the Committee believe that mimicking the expedited review procedure is the best approach?
- What is the Committee's opinion on the risk/benefit analysis of expanded access protocols following the IRB procedure discussed in this presentation?

SACHRP agrees that substantial barriers exist to access to investigational **drugs/biologics** for treatment use, and that the problems are exacerbated for physicians and patients outside of an institutional setting. We offer the following comments and suggestions.

SACHRP notes that as a threshold issue, single patient access use does not involve the conduct of "research" as defined at 45 CFR 46 because there is no intent to develop generalizeable knowledge. Rather, this issue arises out of the FDA prohibition on the use of unapproved drugs, which requires that any use of an investigational drug must currently be considered within the regulatory framework for clinical investigations, primarily 21 CFR Parts 50, 56, and 312.

While the application of the FDA regulations regarding treatment use of investigational drugs/biologics for individual patients (21CFR 312.305 and 312.310) at the single site level with a single patient does not represent research, it is important for IRBs, sponsors and FDA to recognize that the addition of more patients with similar indications begins to raise the need that research related to those indications should occur. Indeed, the Belmont Report is instructive on this point:

> **"When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is 'experimental,' in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.(3)" [Belmont Report]**

In answer to the first four questions **from FDA,** the SACHRP and SOH members have had varying experience with IRB review of single patient expanded access protocols. However, despite our disparate experiences, common themes have emerged. First, reviews of treatment use are administratively burdensome because they involve unique documents and require coordination efforts that differ from the standard IRB review processes. As such, they involve extra time from IRB staff, chairs, and members. They are also difficult from an IRB perspective because they differ from the usual IRB function of reviewing research designed primarily to develop knowledge, as opposed to providing treatment to an identified individual patient. As to the time to review, some IRBs, depending on the setting, are able to review single patient expanded access protocols within a day or two. However, particularly in smaller institutional settings, it is often difficult to convene an ad hoc IRB meeting, as small institutions often have only one scheduled IRB meeting per month. In our collective experience, only independent IRBs charge for the review of single patient expanded access protocols, although some of the independent IRBs waive or reduce the standard IRB fee in these situations, either as standard procedure or upon request. In the experience of the membership of SACHRP and SOH, institution-based IRBs do not charge for these reviews, but we cannot confirm that this is universally true. Expanded access protocols can generally be scheduled ahead of other protocols, but more often the problem is one of arranging an ad hoc IRB meeting to review the expanded access protocol rather than moving that protocol ahead of other protocols in the queue for a scheduled IRB meeting.

SACRHP recommends the way to most immediately address this issue without any change to regulation or guidance is FDA issuance of more specific advice on how to obtain access to treatment use protocols. Currently the FDA website offers only limited advice, and to understand and utilize that advice the reader needs to have a solid understanding of the FDA regulations and their administrative support by FDA. The revised advice should provide a complete overview of the entire issue in one place, and should be understandable to physicians who do not normally conduct research and understandable to non-medically trained patients, as patients and their relatives and loved ones often end up with the task of arranging the expanded access. The advice should include various scenarios. For instance, there are the necessary additional steps to take when the study article is not in the possession of the physician, and must be supplied by the sponsor in a time sensitive nature, and transportation of investigational product must be arranged. The advice should clearly address the role of each party in the process (FDA, sponsor/manufacturer, physician/investigator, IRB, and patient), and delineate in detail what steps must be taken sequentially, and which steps can be taken in any order as long as they are accomplished prior to use of the investigational product. It is often the case that one party or another (FDA, sponsor, investigator) believes that they cannot proceed until one of the other parties takes an action such as providing approval. It would also provide the most immediate assistance in easing the burden of the various parties involved in single patient expanded access protocols if FDA provided a template protocol, consent form, and any other documents necessary for single patient expanded access protocols. Much of the administrative burden associated with these

protocols involves the development of such documents, often from scratch, and subsequent communications between the various involved parties to ensure that the documents are sufficient. This undertaking would provide the most immediate assistance in easing the burden of the various parties involved in single patient expanded access protocols, including patients. SACHRP notes that the American Society of Clinical Oncology (ASCO) issued a press release saying that it would provide guidance of this type, but it is not easy to find on the ASCO website[11], nor is it intuitive for all types of products that one should look to that website.

SACHRP believes that access to investigational drugs could be facilitated substantially if FDA continued to adhere to the "substance" of oversight requirements while being flexible as to "form." That is, certain substantive criteria must be met in order to allow expanded access, and these criteria should be assessed, with satisfaction of these elements documented. However, FDA could exercise enforcement discretion as to the form of review and allow individuals, or committees other than IRBs, to conduct this review, provided the review incorporates the required criteria.

This approach would offer greater flexibility to institutions, health care professionals and the patient community and would likely expedite access for patients, without compromising oversight standards. In addition, this more flexible approach may be better received by many IRBs, which are accustomed to reviewing traditional research protocols and sometimes do not feel comfortable or uniquely qualified to evaluate expanded access use. Given the strong federal policy reasons supporting expanded access, a degree of flexibility as to form of review is consistent with the policy and may even enhance it, as access would be facilitated in practice, and substantive oversight would be maintained or even enhanced by the ability to tailor the review appropriately.

SACHRP believes the most efficient means to implement this flexible approach would be to issue guidance allowing the chair of the IRB, or another appropriate board member, to review the expanded access proposal and provide **an appropriate** opinion. CDRH has already issued guidance to this effect,[12] and if CDER and CBER followed this process as well much of the problem with IRB delay would be resolved.[13] It would need to be clear that this review is not expedited review, and it would be helpful to provide other administrative details, such as whether the single IRB member has the authority to disapprove the expanded use.

Alternatively, a possible approach is to allow IRBs to review treatment use protocols for individual patients through expedited review. SACHRP does not believe that allowing expedited approval of treatment use protocols for individual patients by IRBs is viable unless there is a change to the expedited review regulations at 21 CFR 56.110. In order to be eligible for expedited review, clinical investigations must be minimal risk and must be listed on the separate expedited categories list. These types of test article access rarely involve minimal risk. As the

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[11] See http://www.asco.org/ASCOv2/Press+Center/Latest+News+Releases/ASCO+News/ASCO+and+FDA+Work+Together+to+Help+Physicians+Secure+Investigational%2C+Unapproved+Drugs+For+Seriously+Ill+Patients+in+Need. SACHRP members were not able to find the resource on the ASCO website.

[12] Guidance on IDE Policies and Procedures, Chapter III, online at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080203.pdf.

[13] SACHRP suggests that a change to existing FDA guidance would be useful in accomplishing this. Currently, the Information Sheet entitled "Emergency Use of an Investigational Drug or Biologic" states that "The FDA regulations do not provide for expedited IRB approval in emergency situations. Therefore, "interim," "compassionate," "temporary" or other terms for an expedited approval process are not authorized. An IRB must either convene and give "full board" approval of the emergency use or, if the conditions of 21 CFR 56.102(d) are met and it is not possible to convene a quorum within the time available, the use may proceed without any IRB approval." On-line at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126491.htm. Many IRBs interpret this as not allowing a single board member to review single patient expanded access protocols.

purpose of this access is treatment rather than research, SACHRP believes that a revision to the expedited regulations for this purpose would be a rational approach because, although there may be clinical risks from the treatment, there is no "research risk" involved in such single-patient treatment use.

SACHRP also recommends that there are several alternative approaches the agency might wish to consider. One is to invoke the IRB waiver that currently exists in the FDA regulations at 21CFR56.105. SACHRP recommends that FDA develop a form or format that a treating physician could file with FDA as a "sponsor-investigator" that would request a waiver of IRB review. FDA could develop a process of automatic approval or approval after a brief review of the form. It would be appropriate for the FDA to require the treating sponsor-investigator to notify the IRB with 5 days of such use **and to require some form of patient consent as an additional safeguard.**

Another approach would be to create ready access to a designated single patient access IRB. FDA's existing internal IRB could be that designated IRB. As an alternative to using FDA's internal IRB, FDA could provide a contract or special designation to an existing IRB, but regulatory authority and funding issues would need to be addressed.

Finally, SACHRP notes that FDA could modify 21 CFR 312 so that IRB review of single patient expanded access protocols is not required.

Finally, SACHRP recommends that FDA consider alteration of the current informed consent requirements for clinical investigations when applied to single patient expanded access protocols. Several of the elements of consent do not seem to apply to these protocols.

Regardless of the approach that FDA adopts, FDA and OHRP must work together to ensure that OHRP agrees to the approach.

SACHRP would be pleased to provide further information or opinion on any of the above issues if the input would be of value to the FDA. Patient access to investigational treatments is an critical issue, involving important and difficult principles such as protection of patients from unsafe and ineffective products, while at the same time allowing access for desperately ill patients who have exhausted other options.

Secretary's Advisory Committee on Human Research Protections
February 28-29, 2012
Washington, D.C.

Certification of the Summary of Minutes

I hereby certify that, to the best of my knowledge, the foregoing summary of minutes is accurate and complete.

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Barbara Bierer, M.D., Chair Date